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Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 029.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: University of Iowa OVPRED

Title: Loss of Akirin2 in astrocytes results in disrupted neuronal migration and malformation of the cerebral cortex and cerebellum

Authors: *S. PEEK, P. J. BOSCH, L. C. FULLER, J. A. WEINER
Univ. of Iowa, Iowa City, IA

Abstract: An overlapping series of developmental processes transforms a small population of cells in the embryo into a highly complex, yet precisely organized brain composed of billions of neurons and glia. Disruptions in neurogenesis, neuronal migration, and neuronal and glial differentiation can lead to a variety of congenital disorders ranging from microcephaly to autism. Akirin2 is a small nuclear protein, expressed throughout brain development, that regulates gene expression through interaction with the BAF chromatin remodeling complex. We showed that restricted knockout of *Akirin2* in telencephalic progenitors resulted in agenesis of the cerebral cortex due to decreased progenitor proliferation, aberrant neuronal differentiation, and massive apoptosis (Bosch et al., *Neural Development*, 2016). *Akirin2* remains broadly expressed in the postnatal brain; however, the role it may play in post-mitotic neurons and astrocytes is unclear. We thus crossed floxed *Akirin2* mice to mice harboring the post-mitotic neuron *Synapsin1-Cre* driver or the astrocyte-specific *Gfap-Cre* (line 77.6) driver. *Synapsin1-Cre* knockout mice die within a few days of birth, exhibiting a severe hunched posture and impaired mobility. Nevertheless, the gross structure of the brain appears fairly normal at this immature stage, and both upper and lower layer cortical neurons are generated. Neuronal differentiation appears to be aberrant, as RNAseq analysis of postnatal day (P)0 cortex found 298 significantly upregulated and 366 significantly downregulated transcripts in *Synapsin1-Cre; Akirin2* knockouts. Gene ontology (GO) analysis indicates that downregulated transcripts are associated with cell adhesion, synapse assembly and neuron migration/projection. In contrast, *Gfap-Cre;Akirin2* knockout mice survive and appear outwardly normal until ~P18, after which they exhibit decreased weight and increasingly severe ataxia, culminating in hindlimb paralysis by P25. Loss of *Akirin2* in astrocytes results in gross morphological abnormalities including enlarged lateral ventricles and abnormal cerebellar morphology. The three-layer organization of the cerebellum is disrupted, with Bergmann glia ectopically placed and their radial processes disorganized or absent. Purkinje cell organization is disrupted, and granule cells aberrantly remain in the molecular layer, possibly due to a failure to migrate from the external granule layer. Together,

these data implicate *Akirin2* in the control of gene expression programs essential for postnatal brain development, with a particularly critical role in astrocytes.

Disclosures: S. Peek: None. **P.J. Bosch:** None. **L.C. Fuller:** None. **J.A. Weiner:** None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 029.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: SNF Mobility Grant

Idex France

Title: HopX highlights heterogeneity between and within postnatal SVZ microdomains

Authors: *S. ZWEIFEL
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Abstract: The postnatal SVZ is a region of ongoing germinal activity. For a long time, it was thought to be a homogeneous region regarding the cell types it contains and produces. This point of view is however outdated, as accumulating evidences indicate that NSCs are spatially heterogeneous and generate distinct neural and glial lineages depending of their exact location in the SVZ. We have recently demonstrated an unexpected level of transcriptional heterogeneity that parallels this emergence of distinct lineages from the dorsal and lateral microdomains of the postnatal SVZ. Among others, we found the homeodomain only protein (HopX), to be enriched in the dorsal SVZ, while it is consistently absent from its lateral counterpart. Within the dorsal SVZ its expression follows a gradient with maximal expression at its septal pole. HopX specific transcriptional meta-analysis and co-expression studies indicate a restricted expression of HopX in a subset of NSCs, as well as to cells of the ependymal and astrocytic lineages. Microdissection of the septal vs. lateral regions of the dorsal SVZ followed by transcriptional analysis suggests the existence of an astrogenic (septal) and a neurogenic (lateral) domains within the dorsal SVZ. Consistently, targeted electroporation reveals that these two domains give rise to astrocytes and neurons, respectively. Taken together our data reveal a high level of heterogeneity within postnatal SVZ microdomains with spatial restriction of NSCs that give rise to astrogenic and neuronal lineages.

Disclosures: S. Zweifel: None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 029.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: University of Iowa OVPRED

Title: Loss of Akirin2 in cortical progenitors disrupts gene expression programs that maintain proliferative state and prevent aberrant early differentiation of neurons

Authors: *P. J. BOSCH[1], L. C. FULLER[2], S. PEEK[2], M. PARIDA[2], J. R. MANAK[2], J. A. WEINER[2]
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Abstract: The development of the cerebral cortex is an intricate process that relies on precisely timed patterns of progenitor division, neuron production and migration, and circuit formation. Disruption of these processes or alterations in their coordination can lead to devastating congenital disorders. Akirin2, a nuclear protein that interacts with the BAF chromatin remodeling complex, is expressed in cortical progenitors and is an excellent candidate for coordinating patterns of gene expression during cortical development. Using a floxed *Akirin2* allele and *Emx1-Cre*, we generated cortically-restricted knockout mice, which exhibit a near agenesis of the cerebral cortex; most mutants die at birth, though a few can survive for several weeks. Histological analysis and EdU incorporation assays showed that *Akirin2* mutant cortical progenitors exhibit impaired proliferation and aberrant early cell cycle exit, followed by massive cell death, beginning at embryonic day (E)10.5-11. Few neurons remain, and apical cell-cell junctions in the ventricular zone are disrupted, shown by reduced N-Cadherin and Connexin-43 staining (Bosch et al., *Neural Development*, 2016). To elucidate the mechanisms through which Akirin2 regulates corticogenesis, we performed RNA-seq of control and mutant telencephalon at mid-E10 (about 24 h after *Emx1-Cre* becomes active, but prior to extensive apoptosis), followed by gene ontology (GO) analysis, to identify enriched classes of genes that were differentially expressed. Genes significantly upregulated in *Akirin2* mutant telencephalon included those involved in nervous system development, neuron differentiation, and neuron migration, while those significantly downregulated included those involved in translation and cell-cell adhesion. The transcripts exhibiting the largest fold increases in expression were enriched for neuronal differentiation genes, suggesting that in the absence of Akirin2, progenitors prematurely differentiate. These aberrantly-generated neurons then subsequently undergo apoptosis. Validation by qPCR confirmed that neuron-specific transcripts such as *Tbr1*, *Tbr2*, and *Neurogenin2* are upregulated, and cell-cycle transcripts such as *Myc* and *CyclinD2* are

downregulated, in the *Akirin2* knockout telencephalon. We are currently utilizing *in utero* electroporation to knockout or overexpress Akirin2 in smaller numbers of progenitors at later embryonic ages to confirm its role in maintaining progenitors and inhibiting neuronal differentiation.

Disclosures: **P.J. Bosch:** None. **L.C. Fuller:** None. **S. Peek:** None. **M. Parida:** None. **J.R. Manak:** None. **J.A. Weiner:** None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 029.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NINDS Grant ZIA NS002824-26

Title: The role of Sox21 in regulating embryonic neurogenesis in the olfactory placode

Authors: *N. C. WHITTINGTON, S. WRAY
NINDS, NIH, Bethesda, MD

Abstract: The mechanisms that establish and regulate neuronal fates are important, yet still unknown, developmental issues. During embryonic development, neural crest and ectodermal cells contribute to the olfactory placode and give rise to olfactory sensory neurons, gonadotropin-releasing hormone (GnRH) cells, and olfactory ensheathing cells. This system provides an excellent model to identify the genes that control neurogenesis due to a limited number of final cell types generated in the placode. Sox proteins play important regulatory roles in neurogenesis in both the central nervous system and olfactory placode. Sox2 is a component of the molecular pathway utilized in olfactory placode induction. Sox21 is a Sox2 target and binding partner. Sox21 can regulate neuronal differentiation in the central nervous system based on its level of expression. To determine whether Sox21 may regulate olfactory neurogenesis, its spatiotemporal expression was analyzed in developing mice. Immunocytochemistry data confirmed Sox21 expression in the olfactory placode early in its formation at E9.5. At this stage, Sox21 positive cells are found throughout the placode. From E9.5-E12.5, as the placode invaginates to form the olfactory epithelium and vomeronasal organ, Sox21 expression becomes restricted to dorsal domains of each of these structures. Double labeling was performed for Sox21 and markers to identify cells at different stages of neurogenesis (neural stem cells and progenitors, neuronal precursors and neurons). Sox21 was expressed in progenitor and mitotic cells, and was absent in neuronal precursors, immature neurons, and GnRH cells. Thus, the expression of Sox21 decreased as neurogenesis progressed, consistent with Sox21 having a regulatory role in neurogenesis. Experiments are currently being performed on transgenic Sox21 knock out

embryos to determine whether changes in gene expression, progression of neurogenesis, and/or structure of the olfactory placode occur. This work will define the role of Sox21 in regulating cell fate and patterning during neurogenesis in the olfactory placode.

Disclosures: N.C. Whittington: None. **S. Wray:** None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 029.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: KAKENHI 24240045

KAKENHI 25750395

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

Salt Science Research Foundation

Title: Magnesium signaling activated by GABA facilitates neuronal differentiation in developing neurons

Authors: *R. YAMANAKA[1], Y. SHINDO[2], K. HOTTA[2], K. SUZUKI[3], K. OKA[2]
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Abstract: Structural and functional brain development is fundamentally based on cellular information processing and consequent. To intracellularly integrate information from complex extracellular signals, neurons use many different second messengers simultaneously. Although a role of Mg^{2+} as a second messenger has been revealed in several cells recently, it is still unclear whether the importance of intracellular Mg^{2+} as a signaling molecule in neurons. Excitatory, not inhibitory, GABA actions are essential for maturation of immature neurons and brain development, however the molecular basis of its contribution to the maturation has been little known. Here we show GABA signaling triggers mitochondrial Mg^{2+} release depending on developmental stages in rat hippocampal neurons by using several fluorescent imaging techniques, pharmaceutical characterization and immunological staining. Furthermore, redistribution of Mg^{2+} into cytosol stimulates intracellular signaling pathways, and consequently

facilitates neuronal differentiation. These observations reveal a novel role of Mg^{2+} as an intracellular signal in nervous system and also a key factor in neuronal differentiation.

Disclosures: R. Yamanaka: None. **Y. Shindo:** None. **K. Hotta:** None. **K. Suzuki:** None. **K. Oka:** None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

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Program#/Poster#: 029.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: Korean Research Foundation grant from the Korean government (2012R1A2A01011417)

Chronic Inflammatory Disease Research Center (NRF-2012R1A5A2048183)

Title: Jak3-dependent differentiation in the spinal nestin-positive progenitors

Authors: *E. J. BAIK[1], S. BARUA[2], J.-I. CHUNG[2], A. KIM[2], S.-Y. LEE[2]
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Abstract: During spinal cord development, endogenous progenitors expressing nestin can migrate into the target and differentiate into neurons and other glial cells. Microglial cells also can be derived from $nestin^+$ progenitor cells, even in the adult brain. Previously we reported that knock-down of Jak3 signaling can increase neurogenesis with longer neurite outgrowth in cortical progenitor cells. The present study investigated effect of Jak3 signaling in differentiation from $nestin^+$ progenitor cells using E13.5 spinal cell cultures, In growth factors-enriched conditions, developing neurons could not survive after several days, and also the significant portion of nestin expressing cells transformed into $Iba1^+$ microglial cells, which exponentially increased after 5 days. However, Jak3 inhibition significantly increased $MAP2^+$ neurons and the $Tuj1^+$ growing neurites into the lesion site with little microglial activation. The transcription factors responsible for microgliogenesis, and microglial migration and phagocytosis, such as PU.1, Irf8, CD11b, and Runx1, were strongly regulated by Jak3 signaling. These results indicated that microglial cell differentiation was regulated primarily by Jak3 signaling, and the neurite outgrowth and their maintenance were inversely associated with Jak3-depedent microglial activity.

Disclosures: E.J. Baik: None. **S. Barua:** None. **J. Chung:** None. **A. Kim:** None. **S. Lee:** None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: A.01. Neurogenesis and Gliogenesis

Support: KAKENHI Grant Number 16K18889

Title: An endoplasmic reticulum-associated degradation-related factor SEL1L contribute to neuronal cell fate decision

Authors: *R. SAITO[1,2], K. KAWADA[2], Y. OKUMA[2], N. FUJITA[1], Y. NOMURA[3]
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Abstract: The endoplasmic reticulum (ER) is a primary site of intercellular quality control involved in the recognition and degradation of unfolded proteins. A variety of stresses, including hypoxia and glucose starvation, affects the ER functions and leads to an accumulation of unfolded proteins in the ER, termed ER stress. SEL1L (Suppressor Enhancer Lin12/Notch1 Like) co-localized and forms a complex with a ubiquitin ligase HRD1 in the ER membrane. The HRD1-SEL1L complex is a key component of the endoplasmic reticulum-associated degradation (ERAD) pathway, an ER protein quality control system. Especially, SEL1L acts as a “gate keeper” in the control of *de novo* synthesized proteins. In a previous study, we demonstrated that ER stress induced aberrant neuronal differentiation from NSCs, which associated with the inhibition of neurite outgrowth. Furthermore, we found the possibility that increment of HRD1 expression might be involved in these neurite outgrowth inhibitions. However, it remains unclear whether SEL1L also contribute to neuronal differentiation. To investigate whether ER stress is induced in neuronal differentiation, we semi-quantitatively evaluated the mRNA expression levels of unfolded protein response-related genes using an *in vitro* neuronal differentiation model of P19 cells. At 4 days after stimulation of *all-trans* retinoic acid (ATRA), *Nestin* and several UPR-related genes (*Atf6*, *Xbp1*, *Chop, HRD1* and *Sel1l*) were significantly increased with neuronal differentiation. However, the expression levels of *Atf4* and *Grp78/Bip* were not different in the course of neuronal differentiation. Furthermore, transiently knock-down of SEL1L expression using *Sel1l*-specific siRNA uncovered that the immature neuronal marker βIII-tubulin (also known as Tuj-1) protein level was significantly decreased by SEL1L silencing at 8 days after induction of neuronal differentiation. Consistent with this result, the neuronal progenitor marker *Math1* (also known as *Atoh1*) and the neuronal marker *Math3* (also known as *Atoh3* and *NeuroD4*) mRNA expression levels were significantly suppressed by SEL1L

silencing. These results suggest that SEL1L silencing-induced inhibition of neuronal differentiation could be mediated by *Math1* and *Math3* repression.

Disclosures: R. Saito: None. **K. Kawada:** None. **Y. Okuma:** None. **N. Fujita:** None. **Y. Nomura:** None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01 DC009410

NIH R01 DC014456

The Donita B. Sullivan, MD Professorship

Title: CHD7 and RA regulate neuronal differentiation and inner ear development via independent effects on gene expression

Authors: H. YAO[1], J. M. SKIDMORE[1], S. F. HILL[2], E. D. SPERRY[3], D. L. SWIDERSKI[4], G. J. SANCHEZ[1], M. BOWEN[7], T. SWIGUT[8], D. R. FUENTES[8], L. D. ATTARDI[7], S. IWASE[5], J. WYSOCKA[9], P. C. SCACHERI[10], *D. M. MARTIN[6]
[1]Dept. of Pediatrics and Communicable Dis., [2]Col. of Literature, Science, and the Arts, [3]Med. Scientist Training Program and Departments of Human Genet., [4]Otolaryngology, [5]Human Genet., [6]Human Genetics/Pediatrics, Univ. of Michigan, Ann Arbor, MI; [7]Radiation Oncology - Radiation Biol., Stanford Univ., Palo Alto, CA; [8]Dept. of Chem. and Systems Biol., Stanford Univ. Sch. of Med., Stanford, CA; [9]Dept. of Chem. and Systems Biol. and Dept. of Developmental Biol., Stanford Univ. Sch. of Med. and Howard Hughes Med. Inst., Stanford, CA; [10]Dept. of Genet., Case Western Reserve Univ., Cleveland, OH

Abstract: Proteins that regulate chromatin remodeling govern temporal and spatial gene expression profiles, yet the underlying mechanisms linking their functions in the cell nucleus to cellular phenotypes are not well understood. Importantly, human genetic conditions with overlapping phenotypic features often share underlying pathogenic mechanisms and can provide important insights into the regulation of both cellular-and chromatin-level processes. CHARGE syndrome, an autosomal dominant condition that presents with abnormalities in inner ear and neuronal development including hearing loss and autism spectrum disorder-like behaviors, is caused by heterozygous pathogenic variants in the gene encoding CHD7, an ATP-dependent chromatin remodeler. Interestingly, up- or down-regulation of retinoic acid (RA) signaling during embryogenesis mimics many features of CHARGE syndrome, suggesting CHD7 and RA

may act together to regulate gene expression. Here we explored the biochemical and genetic mechanisms underlying CHD7- and RA-mediated inner ear and neuronal development. Retinoic Acid Response Element (RARE)-reporter activity was unaffected by altered *Chd7* dosage in *Chd7* mutant embryos and in cells transfected with wildtype or mutant *Chd7* expression vectors or with *Chd7*-siRNA. In addition, RA treatment of human SH-SY5Y neuroblastoma cells induced rapid neuronal differentiation but had no major effect on CHD7 protein levels. SH-SY5Y cells exhibited no direct binding between CHD7 and retinoic acid receptor (RAR), either before or after RA treatment, arguing against co-regulation of transcription. Interestingly, RNAseq and qRT-PCR analysis of gene expression in the *Chd7* mutant inner ear showed increased expression of the gene encoding ALDH1A3, an RA synthetase. Notably, loss of *Aldh1a3* had no effect on embryonic inner ear *Chd7* mRNA levels and partially rescued *Chd7* mutant mouse inner ear semicircular canal malformations, consistent with genetic epistasis. *Aldh1a3* expression was also up-regulated in neural progenitor cells derived from *Chd7* homozygous null embryonic stem cells and down-regulated by overexpression of *Chd7*. Taken together, our data suggest that CHD7 and RA regulate neuronal differentiation and inner ear development via independent effects on gene expression, and may help explain the phenotypic overlap that occurs in CHARGE and RA embryopathy.

Disclosures: H. Yao: None. **J.M. Skidmore:** None. **S.F. Hill:** None. **E.D. Sperry:** None. **D.L. Swiderski:** None. **G.J. Sanchez:** None. **M. Bowen:** None. **T. Swigut:** None. **D.R. Fuentes:** None. **L.D. Attardi:** None. **S. Iwase:** None. **J. Wysocka:** None. **P.C. Scacheri:** None. **D.M. Martin:** F. Consulting Fees (e.g., advisory boards); CHARGE Syndrome Foundation.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

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Program#/Poster#: 029.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI Grant Number JP15K18362

Title: Temporal gene expression changes in neural stem cells during brain maturation and aging

Authors: *M. YAMADA[1,2,3], I. IMAYOSHI[2,3,4,5,6]
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Abstract: In the developing mammalian brain, neural stem cells (NSCs) proliferate in the neuroepithelium and sequentially generate several types of neurons in a temporally and spatially regulated manner. Although the majority of neurons are generated in the embryonic period, neurogenesis continues in the postnatal/adult brain. In the postnatal/adult brain, NSCs exist only in two regions, the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone of the hippocampal dentate gyrus. Newly born neurons are integrated into the functional networks of both the olfactory bulb and the hippocampal dentate gyrus, respectively, and there are several evidences that adult neurogenesis is important for various brain functions. The competence of NSCs to continuously generate new neurons over time depends on the coordinated balance of NSC maintenance and differentiation. However, the temporal change of the identity of NSCs has been elusive. To understand the precise mechanism of brain development and adult neurogenesis, it is important to unveil the temporal gene expression changes in NSCs during brain maturation and aging.

Here, we focused on the temporal gene expression changes during brain development and aging of NSCs. In the SVZ of the adult brain, a part of glial fibrillary acidic protein (GFAP)-positive cells function as NSCs (type-B cells). GFAP-positive cells also contain astrocytes, because *GFAP* is one of the glial cell genes. Another NSC-marker protein Nestin is expressed not only in type-B cells but also in type-C transit-amplifying cells. To selectively identify type-B NSCs simultaneously expressing GFAP and Nestin, we utilized GFAP-GFP; Nestin-mCherry-nls double transgenic mouse. We isolated GFP- and mCherry-double positive cells from the adult SVZ (2-, 6-, 18-month old mice) with fluorescence-activated cell sorting (FACS). We also purified NSCs from the embryonic and postnatal brains. We determined gene expression profiles of the isolated NSCs by the RNA-seq analysis.

The temporal gene expression changes of NSCs were compared among embryonic, postnatal and adult stages. We highlighted up-regulated or down-regulated genes by 2-fold or more between the compared stages. In the NSCs derived from the adult brain, many genes related to neurogenesis were down-regulated. By the pathway analysis, we found that large number of genes involved in metabolism were down-regulated during aging. We are trying to identify novel important genes response for the coordinated regulation of NSCs and neurogenesis.

Disclosures: M. Yamada: None. **I. Imayoshi:** None.

Poster

029. Genetic Mechanisms of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 029.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01NS098804

Title: The histone demethylase Kdm6b is required for induction of a mature gene expression program in differentiating cerebellar granule neurons

Authors: U. CHAN[1], F. LIU[1], R. WIJAYATUNGE[1], K. B. SHPARGEL[2], N. J. WAYNE[1], T. R. MAGNUSON[2], *A. E. WEST[3]
[1]Neurobio., Duke Univ., Durham, NC; [2]Genet., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Neurobiol, Duke Univ. Hosp., Durham, NC

Abstract: Neuronal differentiation is comprised of multiple sequential steps that include progenitor proliferation, exit from the cell cycle, migration, synapse formation, and functional maturation. Chromatin regulators play a key role in this process by dynamically remodeling the chromatin landscape to orchestrate the temporal regulation of gene expression programs. The histone H3 lysine 27 (H3K27) demethylase Kdm6b (Jmjd3) has been shown to promote cellular differentiation, yet its physiological functions in neurons remain to be fully determined. We have studied the expression and function of Kdm6b in differentiating granule neurons of the developing postnatal mouse cerebellum. At postnatal day 7, *Kdm6b* is expressed in both the proliferating granule neuron progenitors (GNPs) of the external granule layer (EGL) and the postmitotic cerebellar granule neurons (CGNs) of the inner granule layer (IGL). Interestingly, *Kdm6b* is strongly upregulated in the inner layer of the EGL, which is populated by newly postmitotic CGNs. These data raise the possibility that Kdm6b may play an important role in later stages of CGN differentiation. Consistent with this hypothesis, *Atoh1*-Cre mediated conditional knockout of Kdm6b in GNPs did not disturb the gross morphological development of the cerebellum, which predominantly reflects the proliferation and migration steps of differentiation. Furthermore RNAi-mediated knockdown of *Kdm6b* in cultured GNPs did not alter the induced expression of early neuronal marker genes (*Tubb5*, *Grin2b, Dcx*) upon cell cycle exit. By contrast, knockdown of *Kdm6b* significantly impaired the induction of a late program of neuronal gene expression, which includes gene products (*Grin2c, Gabra1)* required for functional synapse maturation. Loss of *Kdm6b* also impaired the ability of Brain-Derived Neurotrophic Factor (BDNF) to induce expression of *Grin2c* and *Tiam1* in maturing CGNs despite the fact that BDNF was still able to promote survival in *Kdm6b* knockdown CGNs. Taken together these data reveal an important role for Kdm6b in the later steps of CGN maturation and suggest that Kdm6b may work, at least in part, by a permissive chromatin regulatory mechanism that promotes gene sensitivity to BDNF regulation.

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Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: A.01. Neurogenesis and Gliogenesis

Support: postdoctoral fellowship grant from Shriners Hospitals for Children (S.Z.)

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research grants funded by Shriners Hospitals for Children (F.G.)

Title: Role of neural stem factor sox2 in oligodendrocyte development in the postnatal spinal cord

Authors: *S. ZHANG, X. ZHU, X. GUI, P. BANNERMANN, F. GUO
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Abstract: The role of sox2 in the postnatal oligodendrocyte development in the spinal cord was still uncompleted understood. Here we show that Sox2 has dynamic expression during oligodendroglial progenitor cells (OPCs) differentiation. Sox2 is expressed at low level in OPCs and upregulated in newly formed oligodendrocytes (OLs) in the postnatal SPC. Based on these observations, we hypothesize that Sox2 is required for Ols proliferation and differentiation in postnatal SPC development. Using inducible Cre-LoxP conditional knockout (cKO) system to ablate Sox2 in early postnatal OPCs , we demonstrate Sox2 is required for OPC proliferation (evidenced by Ki67 and EdU labeling) and dispensable for maintaining OPC survival (evidenced by active caspase 3 and TUNEL labeling) in vivo during postnatal SPC development. Consistent with a reduction of OPC density, we demonstrated that the density of CC1+ differentiated OLs, including TCF7l2+ premyelinating OLs (Hammond et al., 2015, J Neurosci) was significantly decreased in Sox2 cKO SPC. Previous study has reported that Sox2 is dispensable for the proliferation of embryonic OPCs (Hoffman et al., 2014, Development). Our study suggests that Sox2 function in oligodendroglial lineage cells in a developmental stage-dependent (**embryonic versus postnatal**) manner. Furthermore, we also found myelin related protein expression was transiently inhibited in Sox2 cKO mice. Collectively, our data showed that Sox2 plays an important role in regulating OLs development.

Disclosures: S. Zhang: A. Employment/Salary (full or part-time):; sheng zhang, Institute for Pediatric Regenerative Medicine, Shriners Hospitals for Children, Sacramento, California 95817, Department of Neurology,School of Medicine, University of California, Davis, Sacramento, California, 95817. **X. Zhu:** None. **X. Gui:** None. **P. Bannermann:** None. **F. Guo:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.02/B2

Topic: A.01. Neurogenesis and Gliogenesis

Title: BRN2 is involved in gliogenesis through its tandem amino acid repeats

Authors: *K. HASHIZUME, M. NASU, S. UEDA
Dept. of Biol. Sciences, Grad. Sch. of Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Various mutations have occurred among orthologous genes during evolution. Tandem amino acid repeats (AARs), which are characterized by repeat tract consisting of single amino acid, are common within coding regions of eukaryotic genomes. However, in different species, the frequency and size of AARs vary greatly. In mammals, AARs are abundant in genes encoding transcription factors involved in the brain development. Previous studies have demonstrated the biological function of AARs, and it is suggested that AARs are involved in genetic plasticity driving the evolution. However, whether AARs are useful or not remains controversial, because there are few empirical studies. In our study, to demonstrate the biological significance of AARs, we focused on BRN2 (also known as POU3F2), a transcription factor involved in the neural differentiation, migration, and layer production. Mammalian BRN2 contains three AARs consisted with glycines, glutamines, and prolines, respectively, in its transactivation domain. We investigated the changes that may occur in the presence or absence of AARs using *in vitro* and *in vivo* methods. First, we generated the plasmid vector expressing modified-BRN2, where all AARs are completely deleted and introduced it into Neuro-2a cells to examine the transcriptional regulatory activity by reporter assay. We found that the activity of AARs-deleted BRN2 was significantly higher compared to that of wild-type BRN2, indicating that AARs play an inhibitory role in BRN2. Next, we produced transgenic mice, *Brn2*ΔGQP mice, where BRN2 is replaced with AARs-deleted BRN2. Immunohistochemical analysis revealed that the neurogenesis during embryonic brain development of *Brn2*ΔGQP mice appeared normal. However, interestingly, *Brn2*ΔGQP mice showed the deteriorated astrocyte differentiation, resulting in the decreased number of astrocytes. Furthermore, we carried out the object recognition test, and found that cognitive function was impaired in *Brn2*ΔGQP mice. Together, these results demonstrate that AARs modulate the transcriptional regulatory activation of BRN2 and contribute to brain development and behavior, suggesting biological significance of AARs.

Disclosures: **K. Hashizume:** None. **M. Nasu:** None. **S. Ueda:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.03/B3

Topic: A.01. Neurogenesis and Gliogenesis

Support: DSM Nutritional Products

Title: Essentiality of arachidonic acid (ARA) and docosahexaenoic acid (DHA) in primary neurons, microglia, astrocytes and oligodendrocytes

Authors: *C. M. BUTT[1], M. J. WEISER[1], K. M. WYNALDA-CAMOZZI[1], V. GRIMSHAW[1], N. SALEM, Jr.[2]
[1]HNH-Translational Biol., DSM Nutritional Products, Boulder, CO; [2]Nutritional Lipids, DSM Nutritional Products, Columbia, MD

Abstract: Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are structural and functional components of the developing nervous system, but the dosing of these two lipids for optimal maturation of specific brain cell types has not been established. We hypothesized that the best combinations of ARA and DHA would result in maximal hippocampal neuron growth, maximal inhibition of inflammatory cytokines in microglia, maximal proliferation of astrocytes and oligodendrocytes, and maximal expression of maturation biomarkers such as glial derived neurotrophic factor (GDNF). Primary neurons were prepared from rat hippocampus at embryonic day 18. Primary microglia were isolated from rat cerebral cortex at embryonic day 22. Astrocytes and oligodendrocytes were derived from mixed glial cultures taken from rat cerebral cortex at postnatal day 2. Neurons did not tolerate total ARA+DHA concentrations that exceeded 3 μM, and microglia were activated by total ARA+DHA concentrations greater than 10 μM. In contrast, total ARA+DHA concentrations of 100 μM were not deleterious in astrocytes and oligodendrocytes. Neuron growth was driven by 7-day treatments with DHA, but ARA:DHA ratios of 1:3-1:1 allowed for qualitatively better growth. Treatment with ARA for 24 hours was essential for the inhibition of interleukin-1β, interleukin-6 and tumor necrosis factor-α secretion by microglia activated by lipopolysaccharide, and ARA:DHA ratios of 1:1-3:1 allowed for further reductions of these inflammatory responses. DHA (100 μM) improved GDNF expression in astrocytes as well as early proliferation (2 DIV) of astrocytes and oligodendrocytes, but the ARA:DHA ratio of 1:1 had equivalent effects in these measures. Furthermore, proliferation of astrocytes and oligodendrocytes at later timepoints (5 and 7 DIV, respectively) was best driven by ARA, but, again, the ARA:DHA ratio of 1:1 had equivalent effects. Overall, the findings suggest that, at the acute cellular level, neurons and microglia are more sensitive to high total concentrations of ARA+DHA than astrocytes and oligodendrocytes and that the 1:1 ARA:DHA ratio allows for balanced function of all four cell types.

Disclosures: C.M. Butt: A. Employment/Salary (full or part-time):; DSM Nutritional Products. **M.J. Weiser:** A. Employment/Salary (full or part-time):; DSM Nutritional Products. **K.M. Wynalda-Camozzi:** A. Employment/Salary (full or part-time):; DSM Nutritional Products. **V. Grimshaw:** A. Employment/Salary (full or part-time):; DSM Nutritional Products. **N. Salem:** A. Employment/Salary (full or part-time):; DSM Nutritional Products.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.04/B4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH-NINDS Grant NS083841

NIH Grant GM008688-16

Title: A genome editing approach to studying Pmp22 enhancer functionality

Authors: *H. PANTERA[1,2], J. MORAN[1,2], C. LOPEZ-ANIDO[1,2], J. P. SVAREN[1,2]
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Abstract: The function of the peripheral nervous system is dependent on myelination of peripheral nerve axons by Schwann cells. This process is tightly regulated by a network of transcription factors during early postnatal development. Myelin stability is adversely affected in the most common form of the hereditary peripheral neuropathy called Charcot-Marie-Tooth Disease, resulting in impaired nerve conduction velocity and denervation of muscles in the extremities. This form, classified as CMT1A, is caused by a 1.4 Mb duplication on chromosome 17. This duplication includes the abundantly expressed Schwann cell myelin gene Peripheral Myelin Protein 22 (*Pmp22*), which is associated with multiple disease states in a gene dosage-dependent manner. Previous studies have shown that reducing the expression of *Pmp22* in rodent models of CMT1A results in amelioration of the neuropathy phenotype. In recent work characterizing the mechanisms regulating *Pmp22* transcription, we identified a cluster of putative enhancers approximately 100-160 kb upstream of the *Pmp22* transcription start sites. This upstream cluster was found within a smaller duplication identified in patients with CMT1A-like symptoms, where the *Pmp22* coding region itself was not part of the duplication. In addition, nerve injury experiments show that these enhancers are axon-dependent, as these enhancers become greatly diminished as Pmp22 declines after peripheral nerve injury. This cluster possesses multiple binding sites for factors such as Egr2 and Sox10 that are required for Schwann cell development and myelination. While previous studies in our lab implicate these sites as *Pmp22* enhancers, we wished to test their functional importance in achieving high endogenous levels of *Pmp22* expression. Using genome editing tools including CRISPR/Cas9 in a modified rat Schwann cell line that expresses *Pmp22* at near-physiological levels, we have established clonal lines possessing deletions that include these upstream transcription factor-binding sites. Our data show a decrease in *Pmp22* transcript expression ostensibly due to the loss of these sites, and an even greater decrease in the P1 promoter that is expressed uniquely in Schwann cells. These data show for the first time the requirement of these upstream enhancers for full *Pmp22* expression.

Disclosures: **H. Pantera:** None. **J. Moran:** None. **C. Lopez-Anido:** None. **J.P. Svaren:** 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.; Charcot Marie Tooth Association.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.05/B5

Topic: A.01. Neurogenesis and Gliogenesis

Support: KAKEN Grant 17K08486

Title: Pax6 is expressed in the choroid plexus and subcommissural organ (SCO) during brain development of juvenile mouse

Authors: *S. ARAKI[1], S. YAMANAKA[2], H. INADA[2], N. OSUMI[3]
[1]Dept. of Developmental Neurosci., Tohoku Univercity Sch. of Med., Sendai, Miyagi, Japan; [2]Tohoku Univ., Sendai, Japan; [3]Tohoku Univ. Grad Sch. Med., Sendai, Japan

Abstract: Cerebrospinal fluid (CSF) is a clear and colorless liquid filling cerebral ventricles and subarachnoid space of the brain and the spinal cord. CSF is produced in the choroid plexuses of the lateral, third, and fourth ventricles, and reabsorbed in the arachnoid granulations of the brain and the venous plexus of spinal canal. CSF functions as not only a cushion against physical impact but also a cleaning system for removal of waste product in the brain. CSF is also thought to be as a medium that transports various factors to the whole brain. The breakdown in the CSF homeostasis leads to severe dysfunctions of the brain such as hydrocephalus. Several regions, such as the choroid plexuses, subfornical organ, organum vasculosum laminae terminalis, and pineal gland, are identified as organs to produce the bioactive components in the brain. The subcommissural organ (SCO) is one of these secretory organs, which is located at the entrance of Sylvian aqueduct (Guerra et al., 2015). SCO has been reported to secrete SCO-spondin, transthyretin, and basic fibroblast growth factor. It has been proposed that the SCO could contribute to maintenance of CSF homeostasis and neurogenesis in both fetal and adult rodents. However, the function of SCO remains largely unknown. We focused on Pax6, a transcription factor essential for brain development and neurogenesis, because it is expressed in the SCO and *Pax6* mutant (*Sey*) mouse showed a severe defect in SCO development in the brain at embryonic stage (Estivill-Torrús, et al., 2001). We confirmed that Pax6 has a strong expression in the SCO through the postnatal stages up to P30. Interestingly, Pax6 was expressed in the choroid plexus of the third ventricle but not in the lateral ventricles. These results suggest that Pax6 could play an important role for the maintenance of these organs, contributing to the CSF homeostasis at postnatal brain. Our finding of differential Pax6 expression in the choroid plexuses may also link

to the functional difference between the choroid plexuses in lateral and third ventricles. Since *Sey/Sey* mice die at birth, we are now generating *Pax6* conditional knockout mice using *Pax6f/f* mice (Suzuki et al., 2015) to understand the function of Pax6 in the secretory radial glia that form SCO and choroid plexuses.

Disclosures: S. Araki: None. **S. Yamanaka:** None. **H. Inada:** None. **N. Osumi:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.06/DP01/B6 (Dynamic Poster)

Topic: A.01. Neurogenesis and Gliogenesis

Support: StratNeuro

Vetenskapsrådet grant

Title: Advanced CLARITY method for the analysis of the spatial-temporal progression of peripheral nervous system myelination in mice

Authors: *L. BARTESAGHI[1], C. BELLARDITA[2], O. KIEHN[4], R. CHRAST[3]
[1]Neuorscience, Karolinska Institutet, Solna, Sweden; [3]Dept. of Neurosci. and Dept. of Clin. Neurosci., [2]Karolinska Institutet, Stockholm, Sweden; [4]Dept. of Neuroscience, Karolinska, Stockholm, Sweden

Abstract: ABSTRACT:
Myelin is a spiral extension of the cell membrane of Schwann cells (SCs) in the peripheral nervous system (PNS) and of oligodendrocytes in the central nervous system (CNS) which insulate axons thus increasing the speed of propagation of action potentials. During PNS development, SCs proliferate, associate and migrate along large calibre axons and finally myelinate them. It is known that PNS myelination in mammals starts at around birth, however the spatial aspect of this process remains to be clarified. We used the CLARITY technique in combination with light-sheet microscopy to follow the first steps of PNS myelination choosing as a model mouse sciatic nerve (composed of sensory and motor fibres) and ventral (motor) and dorsal (sensory) roots that branch off the spinal cord from the transitional zone to generate the peripheral nerve. We used antibodies against myelin basic protein that detect myelinating glia in PNS and CNS; against myelin protein zero, a specific marker of PNS myelin, and against neurofilaments that recognizes all neurons/axons. We focused our attention on late embryonic stage E18.5 and early postnatal stages covering the period of initiation of myelination in rodents. Our analysis revealed that myelinating SCs are detectable at first in newborn mice and that they are present more abundantly in the ventral roots. Also in the outgrowing nerve the myelinating

SCs seem to be preferentially associated to motor fibres. These observations indicate that myelination starts in restricted areas before progressively spreading through the PNS, suggesting presence of local instructive signalling that remains to be characterized.

Disclosures: L. Bartesaghi: None. **C. Bellardita:** None. **O. Kiehn:** None. **R. Chrast:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.07/B7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5 F32 NS098647-02

Title: Endothelin-1 signaling in the postnatal subventricular zone regulates oligodendrocyte progenitor cell proliferation and maturation

Authors: *K. ADAMS[1], M. BUGIANI[2], M. S. VAN DER KNAAP[2], V. GALLO[1]
[1]Childrens Natl. Med. Ctr., Washington, DC; [2]VU Univ. Med. Ctr., Amsterdam, Netherlands

Abstract: White matter dysfunction occurs in a wide range of neurodegenerative conditions, including demyelinating diseases such as multiple sclerosis, and a variety of central nervous system insults and pathologies. Demyelination is largely caused by a loss of mature oligodendrocytes (OLs) - glial cells that produce the myelin sheaths that are required for proper synaptic transmission and neuronal function. Recent efforts have focused on promoting OL regeneration from endogenous oligodendrocyte progenitor cells (OPCs) in the subventricular zone (SVZ), with the hope of gaining functional recovery in patients. Our lab previously found that the signaling peptide, Endothelin-1 (ET-1), delays OL maturation after demyelination of the corpus callosum, suggesting that ET-1 is a novel regulator of OL development *in vivo*. To test this hypothesis, the function of ET-1 in the mouse SVZ during normal development and after demyelinating injury was investigated. We found that ET-1 is highly expressed in the SVZ during postnatal development. Ablation of ET-1 in the SVZ reduced the percentage of NG2+ OPCs and Ki67+ OPCs in the SVZ, and increased the number of neuronal progenitors. Pharmacological inhibition and genetic ablation of the Endothelin Receptor Type B (EDNRB) from OPCs replicated these results, reducing the percentage of NG2+ OPCs and Ki67+ OPCs in the postnatal SVZ. These results suggest that ET-1 directly signals to OPCs in the postnatal SVZ to promote and/or maintain OPC proliferation. Lastly, ET-1 was upregulated in the adult human SVZ of patients with Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL). This correlated with an increase in OPCs in the SVZ of CARASAL patients, compared to age-matched controls. Together, these results support the hypothesis that ET-1

signaling regulates OPC development in the postnatal brain and represents a potential therapeutic target for OL regeneration strategies.

Disclosures: K. Adams: None. **M. Bugiani:** None. **M.S. van der Knaap:** None. **V. Gallo:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.08/B8

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Program of Sustainability II (MEYS CR) project no. LQ1605

FNUSA-ICRC no. CZ.1.05/1.1.00/02.0123 (OP VaVpI)

Title: Non discriminant approach to generate human central nervous system cell lineages

Authors: *M. CARNA, V. POZO DEVOTO, V. LACOVICH, M. FEOLE, K. TEXLOVA, G. STOKIN
Translational Neurosci. and Aging Res. Group, Intl. Clin. Res. Ctr. FNUSA-ICRC, Brno, Czech Republic

Abstract: To date, different protocols have been used to differentiate human stem cells into neuronal and glial lineages, however they drive the differentiation towards a specific CNS cell type at the expense of the others. Considering recent evidence indicates that differentiation of CNS cell lineages requires intimate exchange of transcription factors between differentiating cell types, current protocols may not be appropriate for optimal differentiation of neural stem cells (NSCs) into mature CNS cell lineages. To test, whether NSCs can be differentiated into comparable amount of fully differentiated CNS cell lineages, namely neurons, astrocytes and oligodendrocytes, a novel protocol was developed to allow for exchange of all necessary transcription factors and allow for optimal maturation of CNS cell lineages. The medium was designed to mimic brain-like serum-free environment to test cells interactions and functionality. Non discriminant approach was used to examine maturation and functional characteristics of the CNS cell lineages. Changes in differential gene and protein expression patterns (qPCR, FACS), phenotypic diversity (ICC, SEM) and functional assays (MEA, Ca2+, Glutamate uptake, Ensheathing analysis), were compared to demonstrate their physiological responses. This newly designed system significantly improved astrocyte features, enhanced neuronal activity in culture and furthermore robustly promoted myelination. Combination of specific ratios of pure sorted CNS cells was used to study morphological and functional characteristics of mature CNS lineages and their detailed gene analysis uncovered unique cell lineages profiles. These results

indicate that the proposed platform allows optimal maturation and physiological functioning of NSCs derived cells that can be used as powerful tool to study neurobiological impact of glial cell on neural differentiation, development and promote different approaches to study human neurological diseases in vitro.

Disclosures: M. Carna: None. **V. Pozo Devoto:** None. **V. Lacovich:** None. **M. Feole:** None. **K. Texlova:** None. **G. Stokin:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.09/B9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R21-NS096334-01A1

NIH R01-AG051437-01

Title: Microglia progenitor cells in the mouse brain may express Prominin-1 (CD133)

Authors: *K. E. PRATER[1], M. S. ALOI[2], W. SU[1], S. DAVIDSON[1], G. A. GARDEN[2]
[1]Neurol., [2]Dept. of Neurology, Dept. of Pathology, Univ. of Washington, Seattle, WA

Abstract: Neuroinflammation is critical to processes including CNS development, injury, and disease. Microglia are innate immune cells that mediate neuroinflammation. While microglia are self-renewing within the central nervous system, cell-surface markers expressed solely by microglia progenitors have not been identified. Recent studies report that microglia progenitors express Nestin. Here, we hypothesize that Prominin-1 (CD133) is a marker of microglia progenitors. We initially identified CD133 as differentially expressed by microglia progenitors compared to mature microglia. This was accomplished by leveraging our observation that by *ex vivo* flow cytometry, Nestin expressing CD11b+ microglia progenitors are predominantly observed in the low CD45 surface expressing population. Using CD45 to segregate Percoll gradient isolated CD11b+ cells, we generated two populations for RNA sequencing analysis using fluorescence-activated cell sorting (FACS). We observed that one surface marker predominantly expressed by the putative microglia progenitor population was CD133. CD133 is a known marker of multi-potent astrocytic and neural stem cells. It is not known whether CD11b+ microglia progenitors express surface CD133. Using flow cytometry, we observed that in the neonatal mouse cortical culture system used to generate floating microglia from adherent monolayers of mixed glial cultures, CD133 expressing cells are present only in the cell population adherent to the flask surface. Moreover, a population of the adherent cells express mature microglia markers such as CD45 and CD11b in addition to Nestin. In contrast, mature

floating microglia express CD45 and CD11b but do not express Nestin. To isolate CD133 expressing cells *in vivo*, we used 12-16-week-old C57Bl/6 mice from our colony. Prior to FACS, whole forebrain was homogenized and microglia were isolated using a Percoll gradient. We found CD133 expressing cells in the population of microglia-sized cells isolated from the Percoll gradient selection. We are working to determine if CD133 expressing cells isolated using FACS from the adult mouse brain can be cultured to generate new microglia. Being able to identify microglia progenitor cells based on surface markers would allow us to monitor microglia proliferation in the brain throughout disease, development, and injury processes.

Disclosures: K.E. Prater: None. **M.S. Aloi:** None. **W. Su:** None. **S. Davidson:** None. **G.A. Garden:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.10/B10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NCATS - 2UL1TR000433

NIH - RO1NS077730

DMRF

Title: Cell autonomous regulation of CNS myelination by the DYT6 dystonia protein, Thap1

Authors: *D. YELLAJOSHYULA, C.-C. LIANG, S. PAPPAS, W. DAUER
Univ. Of Michigan, Ann Arbor, MI

Abstract: The childhood-onset motor disorder DYT6 dystonia is caused by loss-of-function mutations in the transcription factor THAP1, but the neurodevelopmental processes in which THAP1 participates are unknown. We find that THAP1 plays a critical role in myelination initiation during CNS maturation. Conditional deletion of THAP1 in the CNS retards maturation of the oligodendrocyte (OL) lineage, delaying myelination and causing persistent motor deficits. The CNS myelination defect results from a cell autonomous requirement for THAP1 in the OL lineage, and is clearly recapitulated in the *in vitro* differentiation paradigm of OL progenitor cells purified from *Thap1* null mice. Genome-wide binding studies indicate that THAP1 has significantly high co-occupancy with YY1, a transcription factor that has an essential role in OL maturation. Furthermore, loss of THAP1 function disrupts the DNA occupancy of YY1 at genes co-occupied by these transcription factors. As with YY1, loss of THAP1 results in dysregulation of Id gene expression, which play a critical role in the regulation of myelin genes. These studies

establish a role for THAP1 transcriptional regulation at the inception of myelination, and implicate abnormal timing of myelination in the pathogenesis of childhood-onset dystonia.

Disclosures: **D. Yellajoshyula:** None. **C. Liang:** None. **S. Pappas:** None. **W. Dauer:** None.

Poster

030. Glial Modulation of Neurogenesis

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Topic: A.01. Neurogenesis and Gliogenesis

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Shenzhen Committee for Technological Renovation Grant ZDSY20120617112838879

European Research Council (ERC)-Advanced and ERCProof of Concept Grants

Title: Leucine-rich glioma inactivated 1 promotes oligodendrocyte differentiation and myelination via TSC-mTOR signaling in central nervous system

Authors: *C. SHAO[1], Y. XIE[1,2], L. ZHOU[1], Y. SHEN[1]
[1]Sch. of Medicince Zhejiang Univ., Inst. of Neurosci., Hangzhou Zhejiang, China; [2]Harvard Med. Sch., Dept. of Neurobio., Cambrige, MA

Abstract: Leucine-rich glioma inactivated 1 (Lgi1), a putative tumor suppressor, is tightly associated with autosomal dominant lateral temporal lobe epilepsy. Lgi1 also regulates the myelination of Schwann cells in the peripheral nervous system. However, the function and underlying mechanisms for Lgi1 regulation of oligodendrocyte differentiation and myelination in the central nervous system remain elusive. Importantly, whether Lgi1 is required for myelin maintenance is unknown. Here, we show that Lgi1 is necessary and sufficient for the differentiation of oligodendrocyte precursor cells and is also required for the maintenance of myelinated fibers. The hypomyelination in $Lgi1^{-/-}$ mice attributes to the inhibition of the biosynthesis of lipids and proteins in oligodendrocytes. Moreover, we found that Lgi1 deficiency leads to a decrease in expression of tuberous sclerosis complex 1 and activates mTOR signaling. Together, the present work establishes that Lgi1 is a regulator of oligodendrocyte development

and CNS myelination. Our results yet suggest that Lgi1 deficiency results in reduced expression of myelin proteins and demyelination accompanying the progression of malignant gliomas.

Disclosures: **C. Shao:** None. **Y. Xie:** None. **L. Zhou:** None. **Y. Shen:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.12/B12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF RII Track 1ASSET III, #1457888

NIH INBRE P20GM103429

A-State Arkansas Biosciences Institute

Title: Extracellular environment influences neural stem cell differentiation

Authors: K. SHARMA[1], S. C. PANDANABOINA[1], R. A. KORE[2], R. GRIFFIN[2], *M. SRIVATSAN[1]
[1]Arkansas State Univ., State Univ, AR; [2]Univ. of Arkansas for Med. Sci., Little Rock, AR

Abstract: Neural stem cell (NSC) transplantation for demyelinating diseases has received much attention lately. However, NSCs may differentiate into neurons, astrocytes, and oligodendrocytes (ODCs), and hence it is uncertain if NSCs will become the desired cell type once transplanted. Hence transplantation of fully differentiated functional ODCs may be a better therapeutic option, yet would require huge population of functional ODCs. Evidence shows that NSC differentiation is influenced by the interaction of the stem cells and their extracellular environment (ECM). Although in vitro neural differentiation experiments routinely use poly-d-lysine (PDL) as a substratum, we tested if a natural extracellular matrix (e.g. matrigel) promotes ODC differentiation better than PDL. In addition, exosomes secreted in ECM appear to be effective inter cellular communicators delivering proteins, RNA etc. suggesting exosomes in ECM could promote neural differentiation. Some of the earlier in vitro neural differentiation protocols used glioma conditioned medium in cell culture to promote differentiation suggesting exosomes present in the glioma conditioned medium could enhance differentiation. Therefore we differentiated NPCs in culture with (1) PDL or matrigel as substrates and (2) with the presence or absence of exosomes derived from U87glioma or exosomes derived from U87glioma treated with interleukin 1ß . NSCs from rat E14 were propagated in the presence of basic fibroblast growth factor (bFGF) and platelet derived growth factor alpha (PDGF-A) and differentiated on matrigel and PDL in the presence of thyroxine for ten days. Immunocytochemistry using Rip (ODC) and GFAP (astrocyte) antibodies showed that 91.8%±4.2% were Rip+ cells on matrigel

compared to PDL (19.3%±5.8%). While 66.0%±9.4% of NSCs on PDL remained undifferentiated, such cells were very few on matrigel demonstrating a significant effect of matrigel on ODC differentiation ($F=91.9$, $DF_{3, 28}$, $P<0.001$). Exosomes from untreated or IL1β-treated glioma cells differentiated less number of NSCs into ODCs (3.9%±1.2% and 4.6%±1.0%, respectively). However, surprisingly significantly ($F_{3,28}=209.45$, $p<0.001$) more cells differentiated into astrocytes with exosomes from untreated (35.6%±5.3%) and treated (76.8%±1.2%) glioma cells compared to cultures on matrigel (8.1%±4.2%). Also exosomes from glioma inhibited differentiation and population of undifferentiated cells was higher (60.5%±2.0%) in untreated, 18.6%±5.3% treated) than those on matrigel (0.01%). Are the contents of exosomes derived from glioma cells differentiate NSCs into astrocytes or glioma cells while reducing differentiation?

Disclosures: K. Sharma: None. **S.C. Pandanaboina:** None. **R.A. Kore:** None. **R. Griffin:** None. **M. Srivatsan:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.13/B13

Topic: A.01. Neurogenesis and Gliogenesis

Support: Inserm

CNRS

UPMC

ANR-OLGA

ANR-10-IAIHU-06

NeurATRIS

Novartis

Title: Screening drugs promoting remyelination in Xenopus

Authors: *B. ZALC[1], A. MANNIOUI[2], Q. VAUZANGES[1], J. FINI[3], E. HENRIET[1], S. SEKIZAR[1], L. AZOYAN[1], J.-L. THOMAS[1], D. DUPASQUIER[4], B. DEMENEIX[3], C. GIOVANNANGELI[5]
[1]Sorbonne Universités UPMC; Inserm, CNRS, Paris Cedex 13, France; [2]ICM, Sorbonne Universités UPMC Univ. Paris 06, Inserm, CNRS, Paris, France; [3]CNRS UMR 7221, Muséum

Natl. d'Histoire Naturelle, Paris, France; [4]Watchfrog, Evry, France; [5]CNRS UMR 7196, Muséum Natl. d'Histoire Naturelle, Paris, France

Abstract: In Multiple sclerosis development of screening tools for remyelination-promoting molecules is timely. A *Xenopus* transgenic line allowing conditional ablation of myelinating oligodendrocytes has been adapted for *in vivo* screening of remyelination-favoring molecules. In this transgenic, the green fluorescent protein reporter is fused to *E. coli* nitroreductase and expressed specifically in myelinating oligodendrocytes. Nitroreductase converts the innocuous pro-drug metronidazole to a cytotoxin. Spontaneous remyelination occurs after metronidazole-induced demyelinating responses. As tadpoles are transparent, these events can be monitored *in vivo* and quantified. At the end of metronidazole-induced demyelination, tadpoles were screened in water containing the compounds tested. After 72h remyelination was assayed by counting numbers of oligodendrocytes per optic nerve. Among a battery of molecules tested, siponimod, a dual agonist of sphingosine-1-phosphate receptor 1 and 5, was among the most efficient favoring remyelination. Crispr/cas9 gene editing showed that the promyelinating effect of siponimod involves the sphingosine-1-phosphate receptor 5. This *Xenopus* transgenic line constitutes a simple *in vivo* screening platform for myelin repair therapeutics. We validated several known pro-myelinating compounds, and demonstrated that the strong remyelinating efficacy of siponimod implicates the sphingosine-1-phosphate receptor 5.

Disclosures: B. Zalc: 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.; Novartis. **A. Mannioui:** 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.; novartis. **Q. Vauzanges:** None. **J. Fini:** None. **E. Henriet:** None. **S. Sekizar:** None. **L. Azoyan:** None. **J. Thomas:** None. **D. DuPasquier:** A. Employment/Salary (full or part-time):; WatchFrog. **B. Demeneix:** None. **C. Giovannangeli:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.14/B14

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS088529

Title: A role for the homeobox transcription factor Gsx1 in oligodendrocyte development

Authors: L. A. EHRMAN[1], V. KOHLI[4], D. NARDINI[2], *R. R. WACLAW[3]
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Abstract: Oligodendrocyte development requires temporal changes in gene expression and signaling pathway activation. Multiple lines of evidence suggest that elevations of the RAS/MAPK pathway influence early stages of glial cell development and oligodendrogenesis. We performed RNA sequencing on postnatal optic nerves from two RAS/MAPK GOF mouse models (*Ptpn11*$^{D61G/+}$ and *NF1*$^{loxp/loxp}$;*Olig2*$^{cre/+}$) to identify regulators of oligodendrocyte progenitor cells increased after RAS/MAPK gain of function (GOF) mutation expression. The homeobox transcription factor *Gsx1* was found to be increased in both GOF models. Little is known about *Gsx1* in the telencephalon beyond a compensatory role in the generation of neurons in the absence of *Gsx2* and the promotion of progenitor maturation and expression of early neuronal markers after misexpression. We generated a guinea pig antibody specific to Gsx1 to characterize expression in the embryonic and postnatal brain. Here we show that Gsx1 positive cells are expressed in the postnatal white matter with the largest numbers observed during the first week after birth. Gsx1 positive cells in the white matter express the oligodendrocyte lineage marker Olig2. Specific phenotypes have not been described in the *Gsx1* mutant embryonic and postnatal telencephalon. However, we show that postnatal *Gsx1* mutants display abnormal markers of oligodendrogenesis and reduced expression of mature oligodendrocyte markers (*Plp* and *MBP*). To test the transient expression of Gsx1 in the *Olig2* lineage, we performed a Gsx1 GOF experiment (*Olig2*$^{cre/+;}$*Rosa*$^{tta/+;}$*tetOgsx1*). *Gsx1-GOF* embryos exhibit abnormal ventral forebrain morphology with an expanded medial ganglionic eminence (MGE) and preoptic area. The expression of the MGE marker, Nkx2.1, is decreased but the ventricular zone and glioblast marker, Sox9, is expanded in GOF embryos. Moreover, abnormal clusters of Sox9 and Olig2 positive cells exist away from the ventricular zone at late embryonic time points. Our findings suggest that the transient expression of Gsx1 plays a role in normal oligodendrogenesis.

Disclosures: L.A. Ehrman: None. **V. Kohli:** None. **D. Nardini:** None. **R.R. Waclaw:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.15/B15

Topic: A.01. Neurogenesis and Gliogenesis

Support: H2020-MSCA-IF-2015 707668

Title: Identifying the temporal genetic pathways controlling glial differentiation and patterning using transcriptomics and reverse genetics in zebrafish

Authors: *M. CHARLTON-PERKINS[1], X. ALMEIDA[2], R. MACDONALD[3], W. A. HARRIS[4]
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Abstract: Since their discovery over 150 years ago, the development and function of glia has been grossly under represented in the neural sciences. Their importance in many human neurological diseases has resulted in an explosion of studies into glial development and function. The predominant focus of these studies is on neural cell fate (how neuronal vs. non-neuronal cells are derived from the same epithelia), physiology (the trophic and structural support these cells provide) and regeneration (the capacity of glia to return to an undifferentiated state and replenish a damaged nervous tissue). Studies which are currently lacking, however, are those which focus on the time between glial specification and maturity. During this time window these cells differentiate, take on specific shapes and become appropriately positioned in order to perform the crucial support functions. Indeed, aberrant glial morphology has been noted in several genetic neurodegenerative disorders and thus, our understanding of how this differentiation, shape and positioning is achieved represents a salient research objective. The purpose of this study is to use molecular and genetic tools to identify genes that are indispensable during the glial differentiation process. For this, we have developed a temporal transcriptomic paradigm, in Muller glia of the Zebrafish retina, to identify factors that are uniquely enriched at various different time points within the scope of glial differentiation. Furthermore, we have combined these bioinformatic studies with functional reverse genetic CRISPR screening techniques to assess the physiological importance of each factor as the glia mature in vivo. Through this study, we have established a road map of differentiation through which specified Muller cells differentiate and take on the appropriate shape and position within the retina. Interestingly, many of these candidates have been associated with human neuropathies that are yet to be linked to glial function. Together, this study provides a platform for understanding how glial cell shape and position is determined in the retina. Undoubtedly, these are principles that will be used by other glia in the nervous system and are also likely to provide unique insights into human disease.

Disclosures: M. Charlton-Perkins: None. **X. Almeida:** None. **R. MacDonald:** None. **W.A. Harris:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.16/B16

Topic: A.01. Neurogenesis and Gliogenesis

Support: NMSS-RR-1512-07066

FISM 2015 22/16/F14(VG)

ULITR000075 CTSI-CN ISS(LJC)

Title: Sox17 promotes oligodendrocyte regeneration through reciprocal Wnt and Hedgehog pathway regulation

Authors: *X. MING[1], L.-J. CHEW[2], B. MCELLIN[3], V. GALLO[4]
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Abstract: Sox17 overexpression in CNPSox17 transgenic mice promotes postnatal OL development and prevents OL loss after focal lysolecithin (Lyso) demyelination. Sox17 is expressed in regenerating OLs of adult white matter (WM) lesions, but its function in spontaneous WM repair is not understood. To investigate Sox17 function in oligodendrocyte regeneration, we have characterized demyelinating WM lesions in Sox17 mutant mice. Oligodendroglial-specific Sox17 ablation decreases the formation of postnatal Olig2+ OL lineage cells and delays the regeneration of oligodendrocytes after demyelination. Wnt/beta-catenin signaling that inhibits oligodendrocyte maturation is known to be upregulated in demyelinating lesions. However, activated beta-catenin (ABC) induced by demyelination was not observed in lesions with Sox17 overexpression (CNPSox17). Fewer ABC+Iba1+ microglia and ABC+Caspase3+ cells indicated attenuated damage and reactivity. OL regeneration was increased, evidenced by BrdU+Olig2+ cells. Stereotaxic injection of the b-catenin antagonist CCT036477(CCT) into C57Bl6 mouse lesions did not improve OL generation, but only prevented Caspase3+ cell increase. This suggests that Sox17 provides selective protection through inhibition of b-catenin. Surprisingly, Sox17 was not detected in b-catenin immunoprecipitates from CNPSox17 WM, so that b-catenin inhibition may be indirect. Hedgehog signaling may be involved in the b-catenin related oligodendrogenesis, since GLI2 was previously found to be elevated by Sox17. Indeed, targeted ablation of *Gli2* or Smoothened (*Smo*) changes b-catenin; ABC+ and oligodendrocyte lineage cells in intact WM of both Sox17 wild type and transgenic mice. However, the target ablation of Gli2 decreased these cells in Sox17 wild type mice but increased them in Sox17 transgenic mice, indicating that Sox17 partially depends on Gli2 to regulate b-catenin and oligodendrogenesis. The targeted ablation of Smoothened (*Smo*) shares similar increases or decreases of these cells in both Sox17 wild type and transgenic mice, indicating that Sox17 completely depends on Smoothened to regulate b-catenin and oligodendrogenesis. Stereotaxic application of the SMO agonist SAG in lesions prevented the ABC increase and promoted OPC differentiation. This is consistent with enhanced Smo activation in CNPSox17 lesions, and a large increase in ABC following *Smo* ablation in CNPSox17 lesions. These studies reveal a negative regulatory relationship between Hedgehog and Wnt/b-catenin that is integrated by Sox17 during OL regeneration

Disclosures: **X. Ming:** None. **L. Chew:** None. **B. McEllin:** None. **V. Gallo:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.17/B17

Topic: A.01. Neurogenesis and Gliogenesis

Support: Human Resource Development Group, India

Department of Biotechnology, India

Title: Role of astrocytes in zika virus induced complications in proliferation and differentiation of human neural stem cells

Authors: *R. BHAGAT, JR, H. ARORA, P. SETH
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Abstract: Recent outbreaks and epidemics of ZIKV infection has prompted the World Health Organization to declare a Public Health Emergency of international Concern. Neurotropism of this virus has been confirmed in-vitro and in-vivo in human. Zika virus (ZIKV) infection has been linked to two neurological complications microcephaly and Guillian-Barre syndrome (GBS). ZIKV is of international interest now but very little is known regarding the mechanism of ZIKV induced severe birth defect, microcephaly. Since it is proved that ZIKV directly targets NSCs and glial cells including astrocytes we wanted to probe into molecular mechanism of ZIKV induced disruption. We have employed an in-vitro model system of human neural stem cells (hNSC) and human neural stem cell derived astrocytes to decipher the mechanism. Astrocytes are critical for brain functioning, however their activation is implicated in pathogenesis of various brain disorders. In our study, overexpression of ZIKV proteins in human astrocytes revealed, upregulation of GFAP, ATP release and dysregulation of inflammatory cytokines. We also studied astrocytes interaction with NPCs and differentiating neurons by treating them with astrocytes conditioned media. The clinical condition microcephaly can be explained by exploring three essential processes of cell: cell death, cell migration and cell division. So to understand these processes we employed molecular techniques including neurosphere assay, calcium imaging, FACS and immunocytochemisty. Our study provides details on role of astrocytes in mediating ZIKV induced complications in proliferation and differentiation of human neural stem cells.

Disclosures: R. Bhagat: None. **H. Arora:** None. **P. Seth:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.18/B18

Topic: A.01. Neurogenesis and Gliogenesis

Support: NMSS RR-1512-07066

FISM 2015 22/16/F14

Title: Sox17 regulates Sox2 and TCF7L2/TCF4 induction and promotes oligodendrocyte progenitor response to demyelination

Authors: *L.-J. CHEW[1], B. MCELLIN[1], E. HONG[1], X. MING[1], M. CATRON[1], M. FAUVEAU[2], B. NAIT-OUMESMAR[2], V. GALLO[1]
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Abstract: Sox17 is a member of the Sox F family of factors that is transiently expressed during postnatal oligodendrocyte (OL) development, and which regulates oligodendrocyte progenitor cell differentiation. To understand its function in subcortical white matter (WM), we established a novel floxed Sox17 mouse to characterize the effects of CNPCre-targeted Sox17 ablation in the contexts of OL development and regeneration. Oligodendrogenesis in the Sox17-deficient (cko) WM was found to be decreased at postnatal day 30 (P30), showing reduced Olig2- , CC1 and MAG- expressing OLs. Despite subsequent OL recovery at P60, this change in OLs led to persistent deficits in motor coordination without affecting myelin ultrastructure or the numbers of myelinated axons. The reduction in Olig2+ cells at P30 was preceded by decreased WM Sox2+ and NG2+ progenitors at P18, as well as decreased TCF7L2+ cells. The densities of Ki67+Sox2+ and triple positive Ki67+Sox2+Olig2+ cells were also decreased in the cko at P18, suggesting a role for Sox17 in maintaining Sox2-expressing progenitor cells. Reduced Sox10+ cells were subsequently found in the cko at P30, overlapping with the continued decline of TCF7L2 cells, indicating that Sox17 regulates both interacting factors of OL terminal differentiation. Following focal demyelination in P60 adults, Sox17 ablation significantly decreased the numbers of Olig2+ and MAG+ OLs repopulating the WM lesion area when analyzed at 14 days post lesion (dpl). BrdU pulse chase analysis identified these cells as newly generated OLs. Similar to postnatal development, this reduction in Olig2+ cells in the Sox17 cko WM was preceded by an attenuated induction of Sox2+BrdU+ and TCF7L2+Olig2+ cells at 7 and 10 dpl respectively. These studies reveal a previously uncharacterized developmental function for Sox17 in Sox2 and TCF7L2 regulation in CNS progenitor cells that also impacts OL regeneration. Understanding the mechanisms underlying Sox17 control of OL development and

progenitor cell responses are important for OL regeneration and WM recovery after demyelination injury.

Disclosures: L. Chew: None. **B. McEllin:** None. **E. Hong:** None. **X. Ming:** None. **M. Catron:** None. **M. Fauveau:** None. **B. Nait-Oumesmar:** None. **V. Gallo:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.19/B19

Topic: A.01. Neurogenesis and Gliogenesis

Title: Zinc supplementation prevents white matter and neurobehavioral deficits in high-fat diet-induced obese mice

Authors: T. CHU[1], Y. HUANG[4], G. N. BARNES[2], J. H. FREEDMAN[3], L. CAI[1], *J. CAI[5,1]
[1]Pediatrics, [2]Neurol., [3]Pharmacol. and Toxicology, Univ. of Louisville Sch. of Med., Louisville, KY; [4]Endocrinol. and Metabolism, Danyang People's Hosp., Danyang, China; [5]Pediatrics, Univ. of Louisville Dept. of Pediatrics, Louisville, KY

Abstract: The accumulating evidence from brain imaging studies in elderly, adult and childhood obesity indicate extensive loss of white matter (WM) within the limbic system and those connecting the temporal and frontal lobe. However, the underlying mechanisms and preventive/therapeutic interventions remain little known. In order to mimic obesity occurred in children and young adult, 3-week-old C57BL/6 male mice that brain development is roughly equivalent to human brain at childhood were randomly assigned into four groups, and fed a normal diet (ND)/normal zinc (NZ) , high-fat diet (HFD)/NZ , ND/zinc supplement (ZS), and HFD/ZS respectively for 24 weeks. In brain, MAP2 was suppressed while phosphorylation of tau (Thr231) and NF-H/M was increased in cerebra of HFD-induced obese mice. The expression of synapsin I was inhibited as well. In contrast, HFD increased expressions of PDGFRα and NG2 that are specifically localized in OPCs. GalC and CNPase that are specifically expressed in immature OL were also robustly upregulated. Nevertheless, MBP and PLP - major component proteins in myelin sheath were significantly decreased. It suggests that HFD-induced obesity may stimulate OPC generation and/or proliferation but inhibit OL differentiation. WM in corpus callosum (CC), cingulum, and fornix showed hypomyelination, which was further confirmed by high *g*-ratio in CC. HFD-induced obesity also resulted in deteriorations in conduction of the descending tracts, fine motor coordination, cognitive performance, and increased anxiety-like behavior. Surprisingly, decreased expressions of MBP and PLP, hypomyelination in CC, delayed axonal conduction, and neurobehavioral deficits were partially or completely rectified by ZS. Taken together, these findings suggest that HFD-induced obesity impairs white matter integrity in brain and ZS may remodel brain white matter and neurobehaviors.

Disclosures: **T. Chu:** None. **Y. Huang:** None. **G.N. Barnes:** None. **J.H. Freedman:** None. **L. Cai:** None. **J. Cai:** None.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.20/B20

Topic: A.01. Neurogenesis and Gliogenesis

Title: HMGB1-induced neurite outgrowth in mouse dorsal root ganglion neurons and its inhibition by thrombomodulin

Authors: *Y. NAKATAKE[1], F. SEKIGUCHI[1], M. TSUBOTA[1], R. TSUJITA[1,2], G. HONDA[2], A. KAWABATA[1]
[1]Fac. Pharm., Kindai Univ., Higasi-Osaka, Japan; [2]Asahi Kasei Pharma, Tokyo, Japan

Abstract: High mobility group box 1 (HMGB1), a nuclear protein, once passively released from necrotic cells or actively secreted by activated macrophages etc., plays extensive roles as one of damage-associated-molecular patterns (DAMPs). HMGB1 contains three cysteine residues, Cys^{23}, Cys^{45} and Cys^{106}. In a reduced state, HMGB1 exists as all-thiol HMGB1 (at-HMGB1) that has three Cys residues in the thiol form, and activates the receptor for advanced glycation end products (RAGE). In an oxidized state, at-HMGB1 is transformed into disulfide-HMGB1 (ds-HMGB1) that has a disulfide bound between Cys^{23} and Cys^{45}, which in turn activates Toll-like receptor 4 (TLR4). On the other hands, thrombomodulin (TM) expressed on the membrane surface of vascular endothelial cells adsorbs HMGB1 and promotes its degradation by thrombin, an effect mimicked by recombinant human soluble TM (TMα) that has been approved as a medicine for treatment of disseminated intravascular coagulation (DIC) in Japan. Given that HMGB1 induces neurite outgrowth in rat dorsal root ganglion (DRG) neurons, in the present study, we characterized the effects of HMGB1 in distinct redox states on neurite outgrowth in mouse DRG neurons, and examined the inhibitory effect of TMα in the absence and presence of thrombin. Stimulation with at-HMGB1 for 24 h enhanced neurite outgrowth in a concentration-dependent manner in a range of 0.01-1 μg/ml in mouse DRG neurons, whereas ds-HMGB1 did not have such an effect. The at-HMGB1-induced neurite outgrowth was detected extensively in DRG neurons regardless of the sizes of the diameters, and inhibited by FPS-ZM1, a RAGE antagonist. TMα at 100 nM, but not 1-10 nM, significantly inhibited the at-HMGB1-induced neurite outgrowth. In the presence of thrombin at 1 U/ml, however, TMα even at 10 nM, completely suppressed the at-HMGB1-induced neurite outgrowth, while thrombin at 0.1-1 U/ml alone did not exhibit significant inhibitory effect. In conclusion, these data suggest that at-HMGB1, but not ds-HMGB1, induces neurite outgrowth via activation of RAGE, in mouse DRG

neurons, which is suppressed by TMα itself at high concentrations and by TMα at low concentrations in combination with thrombin.

Disclosures: Y. Nakatake: None. **F. Sekiguchi:** None. **M. Tsubota:** None. **R. Tsujita:** A. Employment/Salary (full or part-time):; Asahi Kasei Pharma. **G. Honda:** A. Employment/Salary (full or part-time):; Asahi Kasei Pharma. **A. Kawabata:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Asahi Kasei Pharma.

Poster

030. Glial Modulation of Neurogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 030.21/B21

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS20078

Title: BMP-responsive protease HTRA1 identifies astrocyte subpopulations and regulates astrocytic development and injury response

Authors: *C.-Y. PENG[1], J. CHEN[1], S. VAN GULDEN[1], T. MCGUIRE[1], C. OKA[2], J. A. KESSLER[1]
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Abstract: Astrocytes perform a wide array of physiological functions including structural support, ion exchange, and neurotransmitter uptake. Despite this diversity, molecular markers that label subpopulations of astrocytes are limited, and mechanisms that generate distinct astrocyte subtypes remain unclear. Here we identified a Bone Morphogenetic Protein (BMP) signaling regulated protein, serine protease High temperature requirement A 1 (HtrA1), as a novel marker of cortical astrocytes, but not of neural stem cells, in the adult mouse forebrain. Genetic ablation of HtrA1 in neural progenitors accelerates astrocyte differentiation. In addition, ablation of HtrA1 in cultured astrocytes leads to altered chondroitin sulfate proteoglycan expression and inhibition of neurite extension, along with increased levels of BMP4. Brain injury induces HtrA1 expression in reactive astrocytes, and loss of HtrA1 leads to an impairment in wound closure accompanied by increased proliferation of endothelial and immune cells. Our findings demonstrate that HtrA1 is differentially expressed in subpopulations of adult mouse forebrain astrocytes, and that HtrA1 plays important roles in astrocytic development and injury response.

Disclosures: C. Peng: None. **J. Chen:** None. **S. Van Gulden:** None. **T. McGuire:** None. **C. Oka:** None. **J.A. Kessler:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.01/B22

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant NS045103

NIH Grant NS072302

KSCHIRT Grant 14-1

KSCHIRT Grant 16-1

KLCR Grant P02 415

NIH Grant P30GM110787

Title: IGF-1 mediated neurogenesis involves a novel RIT1/Akt/Sox2 cascade

Authors: *D. A. ANDRES[1], S. MIR[1], W. CAI[2], S. W. CARLSON[3], K. E. SAATMAN[4]
[1]Mol. & Cell. Biochem., Univ. of Kentucky Col. of Med., Lexington, KY; [2]Joslin Diabetes Center, Harvard Med. Sch., Boston, MA; [3]Neurosurg. and VA Pittsburgh Healthcare Syst., Univ. of Pittsburgh, Pittsburgh, PA; [4]Spinal Cord & Brain Injury Res. Cntr, Univ. Kentucky, Lexington, KY

Abstract: Insulin-like growth factor 1 (IGF-1) is known to have diverse effects on brain structure and function, including the promotion of stem cell proliferation and neurogenesis in the adult dentate gyrus. However, the intracellular pathways downstream of the IGF-1 receptor that contribute to these diverse physiological actions remain relatively uncharacterized. Here, we demonstrate that the Ras-related GTPase, *RIT1*, plays a critical role in IGF-1-dependent neurogenesis. Studies in hippocampal neuronal precursor cells (HNPCs) demonstrate that IGF-1 stimulates a RIT1-dependent increase in Sox2 levels, resulting in pro-neural gene expression and increased cellular proliferation. In this novel cascade, RIT1 stimulates Akt-dependent phosphorylation of Sox2 at T118, leading to its stabilization and transcriptional activation. When compared to wild-type HNPCs, *RIT1*$^{-/-}$ HNPCs show deficient IGF-1-dependent Akt signaling and neuronal differentiation, and accordingly, Sox2-dependent hippocampal neurogenesis is significantly blunted following IGF-1 infusion in knockout (*RIT1*$^{-/-}$) mice. Consistent with a role for RIT1 in the modulation of activity-dependent plasticity, exercise-mediated potentiation of hippocampal neurogenesis is also diminished in *RIT1*$^{-/-}$ mice. Taken together, these data identify the previously uncharacterized IGF1-*RIT1*-Akt-Sox2 signaling pathway as a key component of neurogenic niche sensing, contributing to the regulation of neural stem cell homeostasis.

Disclosures: D.A. Andres: None. **S. Mir:** None. **W. Cai:** None. **S.W. Carlson:** None. **K.E. Saatman:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.02/B23

Topic: A.02. Postnatal Neurogenesis

Title: Exercise-induced apoptotic cell death in the hippocampus

Authors: *M. E. STEVENSON, R. A. SWAIN
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Abstract: Exercise produces numerous benefits in the body and brain. In the brain, it is well established that exercise enhances cognition on tasks such as the Morris water maze. Exercise may exert these effects in part through accelerating neurogenesis, the proliferation and migration of new neurons, in the hippocampus. To support the metabolic requirements of elevated neurogenesis, it is in turn necessary to increase angiogenesis, the sprouting of new vessels from preexisting capillaries. Interestingly, within 24 hours of the onset of aerobic exercise, a population of hippocampal cells undergoes apoptotic cell death. Preliminary findings indicate the dentate gyrus region of the dorsal hippocampus is vulnerable to exercise-induced apoptosis. Unbiased stereology indicated a significant increase in caspase-3 immunohistochemical labeling in the dentate gyrus after rodents voluntarily exercised for 24 hours. Additionally, doublecortin, a marker of migrating neurons, was also elevated in expression after this acute bout of exercise. This cell death, although transient, may be an important signal for neurogenesis and angiogenesis, which temporally follow. Future investigations aim to determine which population of hippocampal cells is most vulnerable to exercise-induced cell death.

Disclosures: M.E. Stevenson: None. **R.A. Swain:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.03/B24

Topic: A.02. Postnatal Neurogenesis

Title: Lipocalin-2 regulates adult neurogenesis and contextual discriminative behaviors

Authors: A. FERREIRA, *J. A. PALHA, B. MARQUES, A. NOVAIS, S. MESQUITA, P. LUDOVICO, M. CORREIA-NEVES, N. SOUSA, J. SOUSA, F. MARQUES
Life and Hlth. Sci. Res. Inst. (ICVS), Sch. of Medicine, Univ. of Minho, Braga, Portugal

Abstract: In the adult mammalian brain, newborn granule cells are continuously integrated into hippocampal circuits, and the fine-tuning of this process is important for hippocampal function. Thus, the identification of factors that control adult neural stem cells (NSCs)maintenance, differentiation and integration is essential. Here we show that the deletion of the iron trafficking protein lipocalin-2(LCN2) induces deficits in NSCs proliferation and commitment, with impact on the hippocampal-dependent contextual feardiscriminative task. Mice deficient in LCN2 present an increase in the NSCs population, as a consequence of a G0/G1 cell cycle arrestinduced by increased endogenous oxidative stress. Of notice, supplementation with the iron-chelating agent deferoxamine rescuesNSCs oxidative stress, promotes cell cycle progression and improves contextual fear conditioning. LCN2 is, therefore, a novel keymodulator of neurogenesis that, through iron, controls NSCs cell cycle progression and death, self-renewal, proliferation anddifferentiation and, ultimately, hippocampal function.

Disclosures: A. Ferreira: None. **J.A. Palha:** None. **B. Marques:** None. **A. Novais:** None. **S. Mesquita:** None. **P. Ludovico:** None. **M. Correia-Neves:** None. **N. Sousa:** None. **J. Sousa:** None. **F. Marques:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.04/B25

Topic: A.02. Postnatal Neurogenesis

Title: Transcriptional Regulation of the RIM1 pomotor by NeuroD1

Authors: N. BASHYAL, T. LEE, I.-S. CHO, Y. LEE, S. KIM, *H. K. SUH-KIM
Dept. of Anat., Ajou Univ, Sch. Med., Suwon, Korea, Republic of

Abstract: NeuroD1 is a basic-helix-loop-helix transcription factor, which is known to regulate cell fate determination, differentiation and survival of neuronal cells, enteroendocrine cells, and pancreatic beta cells. NeuroD1 is expressed abundantly in mature neurons of adult nervous system structures, including olfactory bulbs, hippocampus, cerebellum, inner ear sensory neurons, and retinal sensory neurons. RIM1 (Rab3 interactive molecule-1) is an active zone protein which has a role in synaptic vesicle priming to release neurotransmitter. Previous reports showed that overexpression of NeuroD1 increased the RIM1 and RIM2. Since these proteins are

known to play critical roles in exocytosis of secretory vesicles in neuronal and endocrine cells, NeuroD1 may be a master transcription factor that regulates expression of members of secretory machinery. Here, we report a potential role of NeuroD1 in the regulation of RIM1 transcription in neuronal cells.

Disclosures: **N. Bashyal:** None. **T. Lee:** None. **I. Cho:** None. **Y. Lee:** None. **S. Kim:** None. **H.K. Suh-Kim:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.05/B26

Topic: A.02. Postnatal Neurogenesis

Support: NIH R01 AG055357 (JWH and MCH)

NIH R01 MH097887 (JWH)

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Title: Investigating the role of cyclin G2 and its association with beta-catenin in developing and adult neurons

Authors: A. C. HERGARDEN[1], A. ARACHCHIGE DON[2], M. LE MAROIS[1], T. PATRIARCHI[1], J. W. HELL[1,2], *M. C. HORNE[1,2]
[1]PHarmacology, Univ. of California Davis, Davis, CA; [2]Pharmacol., Univ. of Iowa, Iowa City, IA

Abstract: Cyclin G2 (CycG2) is an unconventional cyclin homolog that antagonizes cellular proliferation. We and others previously showed that CycG2 gene (CCNG2) transcripts are enriched in adult mammalian brain tissue, including the cerebellum. Here, we show that CycG2 is abundantly expressed in the hippocampal and cerebellar neurons of rodents and provide evidence that CycG2 has a functional role in mature non-dividing neurons. In unpublished work, we determined that CCNG2 mRNA levels are substantially increased during cerebellar development, reaching peak levels as cerebellar granule cell (GC) neuron precursors exit the cell cycle and differentiate into neurons. Confocal immunofluorescence microscopy verified that CycG2 protein is expressed in differentiating GC and differentiated hippocampal neurons which were isolated from postnatal day 6 or from embryonic day 18 rats, respectively. This finding is

substantiated by online cDNA microarray and in situ hybridization data confirming that CCNG2 transcripts are most abundant in the cerebellum and hippocampus of human and rodent brains. In agreement with our finding that CycG2 localizes to the synaptosome fraction by differential and size fractionation of brain lysate, immunostaining of rat dissociated hippocampal cultures reveals that CycG2 localizes proximate to synaptic markers such as PSD-95 and Bassoon. As our previous work demonstrated that CycG2 forms a catalytically active complex with PP2A/B' and C subunits in cerebellar tissues, we examined whether CycG2 interacts with other PP2A binding partners, including β-catenin. We obtained strong evidence that CycG2 associates with β-catenin in adult rodent hippocampus and cerebellum. Interestingly, recent studies by others link CycG2 with β-catenin/Wnt signaling in mitotic cell types. In preliminary experiments to investigate other binding partners of β-catenin, we found that CycG2 co-immunoprecipitates with both N-cadherin and α-N-catenin, which suggests that CycG2 may participate in the structural stability of the synapse. Ongoing studies will investigate the consequences of shRNA knockdown of CycG2 on neuronal, synaptic, and dendritic morphology as well as on β-catenin and its binding partners. Here we will present our work to better understand CycG2 function in neurons including analysis of CycG2 subcellular distribution and an investigation of the interactions with β-catenin and other potential binding partners.

Disclosures: **A.C. Hergarden:** None. **A. Arachchige Don:** None. **M. Le Marois:** None. **T. Patriarchi:** None. **J.W. Hell:** None. **M.C. Horne:** None.

Poster

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.06/B27

Topic: A.02. Postnatal Neurogenesis

Support: 5R21NS095351-02

Title: Perinatal hyperoxia impairs hippocampal-dependent learning and memory through activation of GSK3-β

Authors: ***J. ABBAH**[1], C.-M. VACHER[2], L.-J. CHEW[2], V. GALLO[2]
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Abstract: Brain injuries are a frequent occurrence among preterm infants with very low birth weight (<1500g). These may arise from perinatal hyperoxia (HO), where oxidative stress causes brain damage, leading to neurological sequelae such as cognitive impairment, and learning disability. The damage to specific circuits critical for cognitive function, and the cellular and physiological mechanisms underlying the long-term consequences of oxidative stress during

CNS development are presently poorly understood. As the hippocampus is an essential structure for cognitive processing, we determined the impact of oxygen-induced damage on hippocampal development and function after short term exposure to high oxygen tension (80%) in a mouse model of perinatal HO brain injury. Mice exposed to HO displayed reduced memory and learning ability in both spatial memory and object recognition tests. Perinatal HO acutely induced cell death, with reduced dentate progenitor proliferation. The density and morphology of inhibitory interneurons was also altered, accompanied by reduction in both spontaneous and miniature inhibitory postsynaptic currents (IPSCs and mIPSCs) in the CA1 and an increase in excitatory postsynaptic currents (EPSCs). Using gene expression screens and protein analyses, we identified the dysregulation of glycogen synthase 3-beta (GSK 3-β) as a central molecular target underlying HO-induced impairment of postnatal neurogenesis and interneuron dysmaturation. Consequently, downregulation of aberrant GSK 3-β activity reversed the deficit in progenitor cell proliferation, aberrant morphology and density of interneurons with consequent restoration of overall inhibitory tone. This intervention significantly improves hippocampal-dependent cognitive ability.

Disclosures: J. Abbah: None. **C. Vacher:** None. **L. Chew:** None. **V. Gallo:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.07/B28

Topic: A.02. Postnatal Neurogenesis

Title: The effect of MAPK signaling pathway on the transcription capability of NeuroD1

Authors: *T. LEE[1], N. BASHYAL[2], I. CHO[2], J.-M. CHOI[2], Y.-D. LEE[2], S.-S. KIM[2], H.-Y. SUH-KIM[2]
[1]Anatomy/ Ajou Univ., Suwon, Korea, Republic of; [2]Anat., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: NeuroD1 is a transcription factor with a basic-helix-loop motif, which is known to regulate differentiation and survival of neuronal cells, enteroendocrine cells, and pancreatic beta cells. Previous reports showed that the overexpression of NeuroD1 increased the expression of Rab3 interactive molecule-1 (RIM1), RIM2, and Munc 18-1. These proteins are known to play critical roles in exocytosis of secretory vesicles in neuronal and endocrine cells in which NeuroD1 may function as a master transcription factor. To test whether the transcription activity of NeuroD1 is regulated by intracellular signaling molecules, we investigated the effect of MAPK on NeuroD-mediated gene expression. Several NeuroD mutants were tested for their protein stability, transactivation in the presence of MEK inhibitors. We will discuss the how MAPK regulates the functionality of NeuroD1.

Disclosures: **T. Lee:** None. **N. Bashyal:** None. **I. Cho:** None. **J. Choi:** None. **Y. Lee:** None. **S. Kim:** None. **H. Suh-Kim:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

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Topic: A.02. Postnatal Neurogenesis

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Title: Neonatal CX26 removal leads to elevated anxiety

Authors: *Y. LIN[1,2], X. SU[1,2], J. CHEN[1,2], Y. YU[1,2]
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Abstract: Electrical coupling between excitatory neurons exist in the neocortex is developmentally regulated. It is initially prominent but eliminated at later developmental stages when chemical synapses emerge. Although electrical coupling has been proposed to modulate neural circuit development, the evidence linking changes in electrical coupling to alterations in behavior is limited. Here, we generated Emx1-CreER^{+};Cx26-loxP^{+} mouse line, and selectively deleted Connexin 26 (CX26) in the excitatory neurons of the neocortex and hippocampus at postnatal day 1 (P1). We evaluated the anxiety-like behavior in the open field test (OF) and the elevated plus maze test (EPM) .We found that CX26-WT and CX26-cKO mice showed no significant difference in the total distance traveled in the field,indicating CX26 deletion did not impair locomotor activity of mice. And the distance and the time traveled in the center of the open field were significantly reduced in CX26-cKO mice compared to their CX26-WT litter-mates. Instead, CX26-cKO mice spent more time in the corners of the open field. Moreover, in the elevated plus maze test,CX26-cKO mice spent significantly less time in the open arms and had significantly smaller number of entries into the open arms than CX26-WT mice during the 5 minute task. Together, these results suggest that CX26-cKO mice exhibit dominant increase in anxiety-related behavior. However, there were no significant differences between CX26-cKO mice and the CX26-WT mice in Morris water maze and Y-maze tests which are associated with

learning and working memory. In addition, no significant differences were observed between CX26-WT and CX26-cKO mice in tail suspension test and the forced swimming test. Our work provides direct evidence that neonatal CX26 removal leads to elevated anxiety.

Disclosures: **Y. Lin:** None. **X. Su:** None. **J. Chen:** None. **Y. Yu:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.09/B30

Topic: A.02. Postnatal Neurogenesis

Title: Role of Notch 1 signaling in mediating the behavioral effects of adiponectin and chronic stress

Authors: *Z. ZHANG[1], B. LIU[2], X.-Y. LU[2]
[1]Binzhou Med. Univ., Shandong, China; [2]Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX

Abstract: Notch signaling is well known for its role in neural development. Notch signaling components are also expressed in the adult brain including the hippocampus, implicated in the development of depression. Our previous studies have shown that the hippocampus is a target brain region of the adipocyte-derived hormone adiponectin, which exerts antidepressant-like effects in chronically stressed mice. The present study examined the effects of adiponectin and chronic stress on Notch1 signaling. Following central infusion of adiponectin, expression of the Notch1 intracellular domain (NICD) and its downstream target gene Hes1 were increased in the hippocampus. In contrast, chronic unpredictable stress decreased NICD and Hes1 in the hippocampus. Whether Notch signaling mediates adiponectin and chronic stress on depressive behaviors is being under investigation.

Disclosures: **Z. Zhang:** None. **B. Liu:** None. **X. Lu:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

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Program#/Poster#: 031.10/B31

Topic: A.02. Postnatal Neurogenesis

Support: Chinese government

Title: The induced division of the *In situ* intrinsic mature neuron in the neocortex of the aged animals

Authors: *S. LIU, R. LIU, J. MA, N. GUO
Beijing Inst. of Basic Med. Sci., Beijing, China

Abstract: It is generally accepted that adult neuron neurogenesis only occurs at certain region of CNS and only from adult neural stem cells (NSCs). However, in our previous experiment, we had successfully induced intrinsic mature neurons to divide *in vitro*. The inductor tri-iodothyronine (T3) and growth/neurotrophic factor cocktail (cocktail) supplemented with T3 could down-regulate the expression of Necdin, change the subcellular localization of the E2F1 to pericaryon and then activate the expression of the Cyclins and eventually trigger cell cycle entry of primary neurons.

Here we further proved that intrinsic neurons from Prefrontal cortex could be induced to divide *in situ* regardless of age. We microinjected the cocktail supplemented with T3 into the neocortex of the middle-aged and the aged rat and sacrificed them four days afterwards. The cortex was sliced and stained with mature neuron's specific markers and Hoechst. The division rate is about 318±118.86 and 326 neurons/mm^3. All of the dividing neurons are stained with neuron's specific markers but not neuronblast's marker DCX, which proved that no neuronblast is involved in this process. The division-induced experiment was further combined with Brdu staining and shows that the induced neurons and its descendants can last for at least 12 weeks.

To further prove that the dividing neurons are intrinsic neurons, Beads were microinjected into the corticospinal tract of adult rats 10 months prior to the division-induced experiment, in which an inductive cocktail was injected into the primary motor cortex of these rats. A substantial amount of the induced dividing neurons was found to be co-labeled with retrograde tracing Beads and the specific marker of mature neurons. Since Beads will not be taken up by fibers of passage and will be eliminated within a few days, its retrograde tracing capabilities is restricted to a limited time in the injection area. So, the Beads' presence in the dividing neuron indicates that this neuron is a functional intrinsic neuron existed in the neocortex at least 7 or 10 months prior to the induction experiment.

we also failed to detect any DCX positive ells in the neocortex of the experiment subject. The lack of DCX positive neuroblast in aged brains indicates that the frequency of neurogenesis in senescent CNS might be considerably lower than previously expected and may not provide enough newborn neurons to encounter neuron loss during aging. However, in our experiment, the neuron division rate upon induction is consistent regardless of age, indicating that this approach may have a better prospect in preventing brain aging and curing neurodegenerative disorder than neurogenesis from NSCs.

Disclosures: **S. Liu:** None. **R. Liu:** None. **J. Ma:** None. **N. Guo:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.11/B32

Topic: A.02. Postnatal Neurogenesis

Title: Environmental enrichment impacts proliferation but not integration following neurogenesis in aged mice

Authors: *H.-J. CHENG[1], J. D. LUU[2], K. D. MURRAY[3]
[1]UC Davis, Davis, CA; [2]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [3]Psychiatry & Behavioral Sci. and Ctr. for Neurosci., Univ. California Davis, Davis, CA

Abstract: Adult neurogenesis occurs throughout life in the neurogenic niche, the subgranular zone (SGZ) of the hippocampus, but the rate of neurogenesis is significantly reduced in aged brain. In spite of this, remaining newborn neurons maintain the ability to undergo proper morphological maturation and integration into existing neuronal circuitry. Previous reports established that the rate of cell proliferation in SGZ is dramatically increased following environmental enrichment compared to those housed in standard control environment. However, whether this increased proliferation translates into increased synaptic integration of newborn neurons into existing circuits is totally unknown. Using a transgenic Gli1CreER mouse line in combination with various reporter lines, we study the synaptic integration of axons from newborn hippocampal neurons in aged mice. Gli1CreER/Brainbow3 control animals were housed either in a standard cage or in an enriched environment with free access to running wheel, domes, and tunnels. Consistent with previous reports, cellular proliferation within SGZ was significantly elevated following enrichment in both young-adult and aged brains. However, there was no impact on morphometric characteristics of newborn synaptic terminals. No significant change in synaptic bouton density or size on the axons between control and enriched conditions was observed. Our results suggest that while environmental enrichment with exercise can enhance the rate of neurogenesis, mechanisms underlying synaptic integration of these newborn neurons are less likely to be impacted by environment conditions.

Disclosures: H. Cheng: None. **J.D. Luu:** None. **K.D. Murray:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

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Topic: A.02. Postnatal Neurogenesis

Support: National Natural Science Foundation of China #81270511, #81570534

Title: Loss of PINK1 alters adult neural stem cell metabolism and inhibits neurogenesis in the hippocampus of mice

Authors: *H. BUELER[1], S. K. AGNIHOTRI[1], R. SHEN[1], J. LI[2], X. GAO[2]
[1]Harbin Inst. of Technol., Harbin, China; [2]Harbin Med. Univ., Harbin, China

Abstract: Mitochondria are emerging as critical organelles in the regulation of adult hippocampal neurogenesis (AHN), during which neural stem cells (NSCs) generate new granule neurons that integrate into the hippocampus throughout adult life. AHN supports certain cognitive abilities (e.g. pattern separation), and stimulation of AHN counteracts stress-induced affective symptoms in animal models of depression and anxiety. Although abnormal AHN is suspected in many neurodegenerative disorders including Parkinson's disease (PD), the underlying mechanisms are poorly understood. Here we used *PINK1*$^{-/-}$ mice that lack a mitochondrial kinase to study the impact of mitochondrial defects on AHN in a model of recessive PD. We show that reduced oxygen consumption, elevated glycolysis and increased apoptosis of *PINK1*$^{-/-}$ NSCs are associated with impaired neuronal differentiation in vitro and in the brain. In the dentate gyrus of *PINK1*$^{-/-}$ mice, dendritic morphology and maturation of doublecortin-positive (DCX^{+}) neuroblasts are compromised compared to wildtype mice. *In vivo* labeling of NSCs with EdU shows that NSC numbers are normal, but differentiation of NSCs to DCX^{+} neuroblasts and mature NeuN^{+} neurons is impeded in *PINK1*$^{-/-}$ mice. Finally, normal home cage activity and corticosterone levels of *PINK1*$^{-/-}$ exclude reduced physical activity and increased stress as causes for defective AHN. For the first time, we reveal a new and important relationship between mitochondrial deficits and impaired AHN in a genetic model of PD. Stimulating AHN by targeting mitochondria and metabolism may hold promise for treating cognitive dysfunction and affective disorders, and mitigating related symptoms in PD and other neurodegenerative conditions.

Disclosures: H. Bueler: None. **S.K. Agnihotri:** None. **R. Shen:** None. **J. Li:** None. **X. Gao:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

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Topic: A.02. Postnatal Neurogenesis

Support: R01 NS045103

Grant 12-1A

Title: RIT1 gtpase regulates Sox2 transcription and neural induction

Authors: *S. MIR[1], D. ANDRES[1], W. CAI[2]
[1]Mol. and Cell. Biochem., Univ. of Kentucky, Lexington, KY; [2]Harvard Med. Sch., Joslin Diabetes Center, MA

Abstract: Understanding the molecular mechanisms governing neurogenesis is necessary for the development of translational strategies to harness this process for neuronal repair. Here we report that the Ras-related GTPase RIT1 serves to control the sequential proliferation and differentiation of adult hippocampal neural progenitor cells, with *in vivo* expression of active RIT1 driving robust adult neurogenesis. Gene expression profiling analysis demonstrates increased expression of a specific set of transcription factors known to govern adult neurogenesis in response to active RIT1 expression in the hippocampus, including sex-determining region Y-related HMG box 2 (Sox2), a well-established regulator of stem cell self-renewal and neurogenesis. In adult hippocampal neuronal precursor cells, RIT1 controls an Akt-dependent signaling cascade, resulting in the stabilization and transcriptional activation of phosphorylated Sox2. Accordingly, using retroviral transduction, active RIT1 (RIT1 M90I) was able to generate new neurons from the human astrocytes and photoreceptors from the retinal ganglion cells. This study shows a role for RIT1 in relaying niche-derived signals to neural/stem progenitor cells to control transcription of genes involved in the induction of neural fate and neuronal differentiation in multiple cell types.

Disclosures: S. Mir: None. **D. Andres:** None. **W. Cai:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

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Topic: A.02. Postnatal Neurogenesis

Support: NIH R15NS092026-01A1

Title: mTORC1 activation alters the fate of subventricular zone neural stem cells

Authors: *H. NEHL[1], F. LICAUSI[2], N. W. HARTMAN[3]
[1]Biol., Stockton Univ., Howell, NJ; [2]Biol., [3]Biol. Program, Stockton Univ., Galloway, NJ

Abstract: Neural stem cells of the postnatal subventricular zone (SVZ) self-renew and give rise to daughter cells that migrate to the olfactory bulb and differentiate into inhibitory interneurons. Studies have shown that these stem cells are committed to producing neuronal subtypes based on their location in the SVZ. While some of the regional markers have been identified, the molecular mechanisms that guide cell fate specification of SVZ stem cells remain unclear. Recent studies have shown that activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway can drive stem cells in both the embryonic and postnatal SVZ to differentiate into daughter cells. Hyperactivation of mTORC1 can also induce aberrant migration and alter dendritic morphology. Using postnatal electroporation, we transfected neural stem cells in the dorsal, ventral and septal SVZ. Three weeks following electroporation, transfected cells expressing RFP were identified in various olfactory bulb layers. Stem cells from the dorsal SVZ were more likely to produce neurons in the superficial glomerular layer, whereas ventral SVZ cells gave rise to neurons in the deeper layers, primarily granule cells. In addition, we activated mTORC1 in SVZ stem cells by expressing a constitutively active form of the GTPase Rheb (RhebCA). Activation of mTORC1 resulted in misplaced neurons in the corpus callosum and cortex, arising from dorsal SVZ sources, and in the ventral striatum, derived from ventral SVZ stem cells. Transfection with RhebCA increased dendritic complexity in both periglomerular and granule cells in the olfactory bulb. Interestingly, RhebCA increased the production of periglomerular cells from the ventral SVZ at the expense of granule cells, but did not alter the neuronal subtypes from the dorsal SVZ. In addition, mTORC1 activation resulted in a marked increase in the number of TH+ periglomerular neurons at a rate similar to those produced by dorsal stem cells. These results suggest that the effects of mTORC1 activation is dependent upon the regional identity of the neural stem cell, driving overall neurogenesis in the dorsal SVZ while altering the cell fate of ventral SVZ progenitors.

Disclosures: H. Nehl: None. **F. LiCausi:** None. **N.W. Hartman:** None.

Poster

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Title: Postnatal neuron increase in the adult human amygdala is more extensive than in other hominids and associated with expression of genes annotated to neurogenesis

Authors: *N. BARGER[1], M. V. VARGAS[1], T. A. AVINO[2], K. SEMENDEFERI[4], C. M. SCHUMANN[3]
[1]Univ. of California, Davis - MIND Inst., Sacramento, CA; [2]Psychiatry & Behavioral Sci., [3]Psychiatry and Behavioral Sci., UC Davis MIND Inst., Sacramento, CA; [4]Univ. California San Diego, La Jolla, CA

Abstract: The amygdala mediates socioemotional processing, has been linked to social complexity, and is one of few brain structures reported to incorporate new neurons postnatally. Neuron numbers increase through macaque development, but only in the paralaminar region. The influences of this increase on whole amygdala number is unknown. We hypothesize that neurons in the amygdala's basal and lateral nuclei, which incorporate the paralaminar in hominids, would be most likely to show age-related increase in hominids and that this might influence whole amygdala numbers. Additionally, we explored the functional implications of a potential increase in neuron number using genomic data from the Human Brain Atlas. We contrast gene expression in the adult human amygdala with the temporal neocortex because data suggest that neurons in the neocortex are not added postnatally. We tested the fit of 4 statistical models to stereological estimates of mature neuron number in humans 2 to 48 years (n=22) and African apes 9 months to 50 years (n=14). Significant regressions that best explained the variance were chosen as the best fit. Because it is possible that meaningful changes may occur in more limited developmental windows, we also ran the analyses on sample subsets, iteratively decreasing sample composition by 10 year increments. In humans, a linear model best described the relationship between neuron number and age in the whole amygdala and its basal nucleus up to 32 years. In apes, an inverse model (high rate of early increase that plateaus over time) best described basal nucleus data through all but the youngest individuals, peaking between 10 and 20 years. Lateral and amygdala neuron numbers were not significantly associated with age in the ape sample. Subsequently, 985 genes with higher expression in the amygdala than temporal cortex (t-test with FDR correction, $p \leq 0.05$, foldchange ≥ 2) were subjected to a Gene Ontology Over-Representation analysis. Significant over-representation of the functional categories neurogenesis, neuron generation, and neuron differentiation were highlighted (Hypergeometric test, Bonferroni correction, $p \leq 0.001$). Quantitative postmortem and genomic data provide support for a pattern of age-related increase in neuron number in the amygdala of higher primates. Humans and apes share pattern of neuron increase in the basal nucleus. Humans, particularly, exhibit a protracted period of neuron increase into the third decade of life which was also apparent in whole amygdala numbers. We speculate that this extensive developmental period could support the extended period of cultural and social learning characterizing our species.

Disclosures: **N. Barger:** None. **M.V. Vargas:** None. **T.A. Avino:** None. **K. Semendeferi:** None. **C.M. Schumann:** None.

Poster

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Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant MH087473

Title: Valine-321-leucine mutation in Neuregulin 1 disrupts adult hippocampal neurogenesis and alters anxiety- & depression-like behavior

Authors: ***A. JONE**[1,2], L. W. ROLE[3,2], D. A. TALMAGE[4,2]
[1]Program in Neurosci., [2]Ctr. for Nervous Syst. Disorders, [3]Neurobio. & Behavior, [4]Pharmacol. Sci., Stony Brook Univ., Stony Brook, NY

Abstract: A single-nucleotide polymorphism in Neuregulin 1 (Nrg1) resulting in a valine-to-leucine substitution at residue 321 has been associated with psychosis and schizophrenia. At least one of the neuron-specific isoforms of Neuregulin 1, Type III Nrg1, undergoes regulated intramembrane proteolysis (RIP) that results in the release of a carboxyl-terminal intracellular domain (ICD), which can translocate to the nucleus. Nuclear signaling of the ICD has been implicated in the regulation of neuronal development, including dendritic arborization in the central nervous system and neural stem cell differentiation. Notably, the valine at residue 321 is a site for γ-secretase cleavage, and the valine-321-leucine (V321L) substitution disrupts Type III Nrg1 RIP and subsequent ICD nuclear signaling *in vitro*.
Young adult mice with the V321L mutation exhibit abnormal adult hippocampal neurogenesis, including decreased neural stem cell proliferation and cell cycle reentry. Ongoing studies are underway to determine whether neural fate specification is aberrant in the mutant dentate gyrus. Furthermore, preliminary studies indicate the mutant mice show aberrant anxiety- and depression-like behavior, as measured by the open field test, elevated plus maze, novelty-suppressed feeding, and tail suspension test.

Disclosures: **A. Jone:** None. **L.W. Role:** None. **D.A. Talmage:** None.

Poster

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Topic: A.02. Postnatal Neurogenesis

Support: NIMH MH103455

Title: Temporally distinct roles for Cyfip1 at synapses

Authors: *K. L. SZABLA[1], O. BOZDAGI-GUNAL[2], D. L. BENSON[1]
[1]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Psychiatry, Rutgers Univ. Med. Sch., Newark, NJ

Abstract: Copy number variation (CNV) at the 15q11.2 region, which includes a gene that encodes Cytoplasmic FMRP Interacting Protein 1 (Cyfip1), is a replicated risk factor for autism, intellectual disability, and schizophrenia. Cyfip1 is expressed predominantly in the hippocampus and has two independent functions: (1) the repression cap-dependent translation and (2) the facilitation of the polymerization of actin filaments at the plasmalemma as an essential component of the WAVE regulatory complex (WRC). Regulation of both cap-dependent translation and the actin cytoskeleton are known to be important for synapse assembly, morphology, and plasticity, but Cyfip1's roles in these processes are poorly understood. In the current study, we used a mouse model that is haploinsufficient for *Cyfip1* in order to examine the differential impact of reduced Cyfip1 expression at young and mature synapses. Newly formed synapses are assembled on an actin-based frame, and consistent with this strong reliance on F-actin, we have shown previously that early postnatal neurons (~P10) with reduced Cyfip1 levels show an increase in presynaptic vesicle release probability in hippocampal neurons that can be completely reversed by restoring WRC function. Here we show that assembly of postsynaptic scaffolding is also affected at young synapses: Biochemical fractionation reveals greatly reduced levels of scaffolding proteins including PSD95 in synaptic fractions *Cyfip1*$^{+/-}$ mice compared to WT, littermate controls with no change in overall levels of protein expression. These data suggest that reductions in Cyfip1 could reduce the pace of synaptogenesis during development. However, immunolabeling in tissue sections from P10 mice show the density of synapses estimated by the clustering of pre- and postsynaptic proteins appears unchanged in neurons having reduced Cyfip1 levels, suggesting that postsynaptic proteins are generated and targeted to synaptic sites, but are abnormally tethered. Since synapse dependence on an F-actin-based structure is developmentally transient, we asked whether mature synapse organization recovers in the absence of Cyfip1. The data show that PSD95 levels in synapse fractions from mature mice with reduced Cyfip1 are similar to WT controls. Nevertheless, synapse composition and plasticity remains permanently disrupted. Taken together, our data suggest that defects in early

synapse formation in mice having reduced levels of *Cyfip1*$^{+/-}$ can have lasting consequences and support an early and essential role for Cyfip1 in the generation of normally functioning synapses which may contribute to neuropsychiatric and/or neurodevelopmental disorders.

Disclosures: K.L. Szabla: None. **O. Bozdagi-Gunal:** None. **D.L. Benson:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 031.18/B39

Topic: A.02. Postnatal Neurogenesis

Support: R01 DC009026

5R56DC008295

Title: Chronic inflammation causes olfactory neural stem cell dysfunction through NF-κB signaling

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Abstract: Chronic rhinosinusitis is the most common cause of olfactory loss, but the underlying pathophysiologic mechanisms are unclear. We have previously reported that a mouse genetic model of chronic olfactory inflammation is characterized by olfactory neuronal death and inhibition of neurogenesis. In this study, we have investigated neural stem cell dynamics in that model and in olfactory tissue from chronic rhinosinusitis patients. We observe that the production of inflammatory cytokines and chemokines by activated basal cells is associated with proliferation of inflammatory cells in situ, suggesting that basal cells participate in local immune regulation. Genetic ablation in horizontal basal cells of RelA/p65, the transcriptional activator of the NF-κB pathway, retards the inflammatory response and maintains HBC stem cell capacity. These data point towards an essential role of intact NF-κB signaling in regulating cross talk between neural stem cells and the immune system in olfactory mucosa. Our study reveals a previously unrecognized molecular mechanism linking neural stem cell dysfunction and olfactory loss.

Disclosures: M. Chen: None. **R.R. Reed:** None. **A.P. Lane:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

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Topic: A.02. Postnatal Neurogenesis

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Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED) (Jesús Ávila)

Title: Novel function of Tau in regulating the effects of external stimuli on adult hippocampal neurogenesis

Authors: *N. PALLAS-BAZARRA[1,2], J. JURADO-ARJONA[1,2], J. TERREROS-RONCAL[1,2], M. NAVARRETE[1], J. A. ESTEBAN[1], F. HERNÁNDEZ[1,3], J. ÁVILA[1,2], M. LLORENS-MARTÍN[1,2,3]
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Abstract: Tau is a microtubule-associated protein found mainly in axons. However, its presence in dendrites and dendritic spines has acquired special relevance due to its involvement in synaptic plasticity. One of the most drastic examples of plasticity in the brain is the addition of new neurons to a preexisting circuitry during the adulthood. Noteworthy, the addition of new neurons to the hippocampal circuit is regulated by numerous external factors, thus conferring an outstanding degree of plasticity to the network. Interestingly, alterations in adult hippocampal neurogenesis appear to be a relevant neuropathological feature of a group of neurodegenerative diseases known as tauopathies, characterized by impaired Tau metabolism. Thus, we aimed to investigate the role of Tau in the regulation of this process exerted by both detrimental (acute stress) and stimulatory (environmental enrichment, EE) external stimuli. By using a Tau *knockout* mice model (Dawson et al, 2001), we demonstrate that Tau plays a novel *in vivo* role in the morphological and synaptic maturation of newborn granule neurons under basal conditions. Moreover, our data reveal that Tau deficiency prevents the selective apoptosis of immature granule neurons caused by acute stress. What´s more, it protects newborn neurons from the

stress-induced dendritic atrophy and loss of postsynaptic densities (PSDs). Strikingly, Tau also regulates the increase in newborn neuron survival triggered by EE. Furthermore, newborn granule neurons from Tau *knockout* mice do not show any stimulatory effect on dendritic development or on PSD generation.
Thus, this work reveals a novel role of Tau in the maturation of newborn granule neurons *in vivo* under basal conditions. Furthermore, we provide evidence that Tau regulates the effects of external stimuli on adult hippocampal neurogenesis, since newborn granule neurons from Tau *knockout* mice are insensitive to the modulation exerted by both stimulatory and detrimental stimuli.

Disclosures: **N. Pallas-Bazarra:** None. **J. Jurado-Arjona:** None. **J. Terreros-Roncal:** None. **M. Navarrete:** None. **J.A. Esteban:** None. **F. Hernández:** None. **J. Ávila:** None. **M. Llorens-Martín:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

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Program#/Poster#: 031.20/B41

Topic: A.02. Postnatal Neurogenesis

Support: NSF-IOS #1656103

NSF-IOS #1456918

Staley Fellowship, Wellesley College

Title: The immune system and adult neurogenesis in a crustacean brain: Semi-granular hemocytes are neural precursors

Authors: *J. L. BENTON, K. M. BANSON, B. S. BELTZ
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Abstract: New neurons are generated in the brains of adult decapod crustaceans. However, the neural precursors in crayfish, which reside in a neurogenic niche, are not self-renewing and must be replenished. The innate immune system is one source of these neural precursors, through the production of semi-granular blood cells (hemocytes). Adoptive transfers of these hemocytes have shown that these are attracted to the neurogenic niche, where they divide and their daughters migrate to brain cell clusters 9 and 10 where adult-born neurons differentiate. Our recent experiments have characterized morphological and molecular features of the two major hemocyte classes (granular and semi-granular cells), and have tested the cytokine-regulated release of these cells from the immune system in vivo and in vitro. Further, the biasing of the semi-granular hemocytes towards a neural fate by specific brain regions and molecules has been

explored. The aim of current experiments is to examine molecular markers of differentiation in adoptively transferred hemocytes that have been treated with agents that bias these towards a neural fate.

Disclosures: **J.L. Benton:** None. **K.M. Banson:** None. **B.S. Beltz:** None.

Poster

031. Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavior

Location: Halls A-C

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Topic: A.02. Postnatal Neurogenesis

Support: NSF-IOS #1656103 (BSB)

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Deutsche Forschungsgemeinschaft (DFG): BR5039/1-1 (GB)

Deutsche Forschungsgemeinschaft (DFG):SCHW1810/1-1 (MS)

Title: First insights into the genetic network underlying embryonic and adult neurogenesis in procambarid crayfish: Using gene expression studies to document the differentiation of hemocytes into neurons during life-long neurogenesis

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Abstract: Two decades after its discovery, the system producing adult-born neurons in the midbrain of decapod crustaceans has emerged as one of the best understood models of adult neurogenesis in invertebrates. The neurogenic system in crayfish has proved particularly suitable for various *in vivo* and *in vitro* approaches due to its accessibility on the brain's surface, relative anatomical simplicity, and the spatial separation of neural precursors as they divide and migrate. As a result, studies on *Procambarus clarkii* have recently provided compelling evidence for the lack of *bona fide* neural stem cells (NSCs) in the adult neurogenic niche, suggesting instead the replenishment of its neural precursor pool by blood cells (hemocytes) generated by the innate immune system. In contrast to this intriguing finding in adults, embryonic neurogenesis is driven by "canonical" NSCs that are readily identifiable based on their size and asymmetric divisions. In the present study, we aim to illuminate the genetic network underlying "canonical" embryonic and "non-canonical" adult neurogenesis in crayfish, in order to better characterize the neural precursor types involved in these pathways. We also want to follow the differentiation of

hemocytes towards a neural fate during adult neurogenesis at the molecular level. For this purpose, we generated transcriptome data for *P. clarkii* by next-generation sequencing and *de novo* assembly and identified genes/gene families known to play key roles in arthropod neurogenesis (e.g., in *Drosophila*), such as *SoxB, Achaete-Scute-Complex*, and *Snail* transcription factors (TFs), the neural determinant *Prospero* and the neuronal marker *Elav*. We then performed *in situ* hybridizations with riboprobes on embryos and adult brains, the latter in combination with *in vivo* cell proliferation markers. Our embryonic data confirm the expression of the target genes in the expected neurogenic regions and cell types, as predicted by studies on other arthropods. Further, we show that several – but apparently not all – of these genes are also expressed in different parts of the adult system, including a *SoxB* TF in the niche, a *Snail* TF in a subpopulation of niche cells and migrating neural precursors, and *Elav* in more advanced neural precursors and differentiated neurons. This is one of the first studies on crustaceans to address neurogenic gene expression at the cellular level. We demonstrate the suitability of this approach for characterizing different cell types along the embryonic and adult neurogenic pathways, which makes it a first crucial step towards unraveling the genetic network governing the neural differentiation of hemocytes in the adult crayfish brain.

Disclosures: G. Brenneis: None. **M. Schwentner:** None. **J.L. Benton:** None. **B.S. Beltz:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.01/B43

Topic: A.03. Stem Cells and Reprogramming

Title: UiPSC model of an autistic child with photographic memory

Authors: *J. SONG[1], Y. ZHOU[3], W. LI[2]
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Abstract: Autism spectrum disorders (ASDs) are a heterogeneous group of complex neurodevelopmental disorders that have some core symptoms, including social interaction impairment, communication deficits, restricted interest, and repetitive behaviors. Despite numerous genome studies have identified hundreds of candidate genes that may cause or predispose children to ASD, the pathogenesis of idiopathic ASD still remain elusive. In addition, it is difficult to obtain children's post-mortem brain samples to analyze. So, the human induced pluripotent stem cells (iPSCs) technology provided a powerful tool for modeling human pathology that could be used to understand the underlying causes of ASD. We modeled urinary iPSCs (UiPSCs) from exfoliated renal epithelial cells present in children's urine samples.

Neurodevelopmental disorders are often characterized by cellular defects apparent at early stages in life. Especially ASDs are early-onset neurodevelopmental disorders. Here we generated UiPSCs from an autistic child with photographic memory and an unrelated healthy control, then researched synaptic plasticity and the excitation-inhibition (E-I) balance of UiPSCs-derived forebrain neurons. We also analysed the exomic mutations of the sample family and the control. UiPSCs from younger donors has less exomic mutations and epigenetic signatures, which is our study original notion. These neurons express different densities of neuronal subtype markers of different cortical layers among UiPSC lines. Electrophysiological recordings of neurons did not show any classic action potentials elicited by depolarizing current injections at 4 weeks after differentiation among all cell lines. And resting potentials of ASD's UiPSCs-derived neurons are not unanimous compared to the control. Our data suggest that neurons of ASD are nonsynchronous in neuronal development.

Disclosures: **J. Song:** None. **Y. Zhou:** None. **W. Li:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

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Topic: A.03. Stem Cells and Reprogramming

Support: Heinz C. Prechter Bipolar Research Fund

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Kelly Elizabeth Beld Fund

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Title: Dysregulation of miRNAs in iPSC-derived neurons from patients with bipolar disorder

Authors: *M. BAME[1], M. MCINNIS[2], S. O'SHEA[3]
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Abstract: Bipolar disorder (BP) is a complex condition characterized by severe fluctuations in mood for which underlying pathological mechanisms remain unclear. The average age of onset of BP is 25 years of age and stressful life events typically precede the first episode. Family and twin studies have identified a genetic component to the disorder, but a single causative gene has yet to be identified. Genome wide linkage studies have identified 16 potential regions spread over 13 different chromosomes to be associated with BP, while genome wide association studies

have identified very few variants which are associated with only a negligible risk of developing BP. A potential mechanistic link to these findings is microRNA dysregulation. MicroRNAs (miRNA) are small, non-coding RNAs approximately 20 nucleotides in length that are responsible for the post-translational regulation of multiple genes, by binding to RNAs and interfering with translation. These RNAs are believed to regulate 70-90% of human genes and have been shown to play important roles in neural development, as well as in the adult brain. Animal studies have shown that environmental stress alters miRNA expression in the brain in a regionally specific fashion, and that miRNAs can modulate synaptic strength and protein translation in response to synaptic activation. Several miRNAs have been found to be dysregulated in postmortem studies of brain tissue isolated from bipolar patients, suggesting there may be miRNA processing defects. Because there are no cellular models of BP, we have taken advantage of the recent discovery that somatic cells can be reprogrammed to pluripotency then directed to form the full complement of neural cells. We have identified 59 miRNAs involved in a wide range of cellular functions, including neuronal development, homeostasis, and signaling as significantly dysregulated in BP iPSC neurons. We have validated 6 miRNAs that were elevated and 2 miRNAs that were lower in BP derived neurons. GO analysis of miRNAs significantly elevated in BP derived neurons show that these miRNAs are involved in regulating a wide variety of cellular pathways, cell proliferation and adhesion, toll-like receptor signaling, cell junction and extracellular matrix organization, phospholipase C activity, and inositol phosphate metabolism. Pathway analysis suggests that many of the genes regulated are involved in signaling pathways that have been implicated in bipolar disorder, such as glutamatergic and GABAergic synapses. We are currently validating a variety of potential gene targets of some of these miRNAs, including SYT4, BDNF, RELN, and ANK3.

Disclosures: **M. Bame:** None. **M. McInnis:** None. **S. O'Shea:** F. Consulting Fees (e.g., advisory boards); Genentech, Inc..

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.03/B45

Topic: A.03. Stem Cells and Reprogramming

Support: Governor’s Council for Medical Research and Treatment of Autism Pilot Grant CAUT15APL041

Nancy Lurie Marks Family Foundation

Title: Neural precursor cells from 16p11.2 deletion patients exhibit enhanced proliferation and altered FGF mitogenic activity

Authors: *R. J. CONNACHER[1], M. WILLIAMS[4], S. PREM[2], J. H. MILLONIG[5], E. M. DICICCO-BLOOM[3]
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Abstract: Autism genetic etiology is heterogeneous and complex. Within this population, up to 1% contain a copy number variation (CNV) within the 16p11.2 (16p) chromosomal region, exhibiting various degrees of ASD symptoms. This CNV affects one copy of 27 genes, including MAPK3 encoding for ERK1. Extracellular factors can signal through ERK to stimulate proliferation and growth during development. Likewise alterations in copies of ERK1 which can lead to ERK dysregulation, as seen in the 16p deletion mice, can impact brain development. Additionally, humans with this microdeletion often have macrocephaly, suggesting growth phenotypes during development due to the 16p CNV.
Our studies investigated iPSC derived neural precursor cells (NPCs) from 3 individuals with the 16p11.2 deletion compared to 3 unaffected age matched controls. The 16p individuals were diagnosed with ASD with varying degrees of severity, as well as one exhibiting macrocephaly. We hypothesized that 16p NPCs would exhibit a proliferation phenotype and altered ERK signaling. Studies are performed on NPC cultures derived from at least two iPSC clones per individual. DNA synthesis is assessed by measuring tritiated thymidine incorporation after a 2h pulse at 48h in vitro. Preliminary studies of 16p NPCs indicated two-fold greater DNA synthesis compared to the 3 unaffected age matched controls. Exposure to extracellular factor FGF, a well-known neurogenic regulator and stimulator of ERK, elicited increased DNA synthesis in both 16p and unaffected control NPCs. Interestingly, the magnitude of FGF-induced DNA synthesis varied according to patient disease severity; NPCs from more severely autistic individuals had a blunted FGF-induced increase while the less severe 16p individual with Aspergers exhibited stimulations similar to unaffected controls. Preliminary studies also measured cellular proliferation and survival by cell counts at 2, 4, and 6 days. Although 16p and control counts were similar after 2 days, there was an 80% greater increase in total cell numbers in 16p NPCs compared to controls by day 6. Preliminary analysis of total ERK1 protein in 16p NPCs revealed a greater than 50% reduction compared to controls. Initial analyses of 16p P-ERK protein revealed a 1.5 fold greater increase from baseline after FGF exposure compared to unaffected individuals. These data suggest that 16p NPCs exhibit greater proliferation compared to unaffected controls as well as altered ERK signaling and mitogenic activity.

Disclosures: R.J. Connacher: None. **M. Williams:** None. **S. Prem:** None. **J.H. Millonig:** None. **E.M. DiCicco-Bloom:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.04/B46

Topic: A.03. Stem Cells and Reprogramming

Support: NJ Governor's Council for Medical Research and Treatment of Autism Pilot Grant CAUT15APL041

Nancy Lurie Marks Family Foundation

Title: Idiopathic and 16p.11.2 deletion autism neural precursor cells exhibit differential neurite outgrowth phenotypes

Authors: *C. C. PENG[1], S. PREM[1], R. J. CONNACHER[2], M. HALE[4], J. H. MILLONIG[5], E. M. DICICCO-BLOOM[3]
[2]Neurosci. and Cell Biol., [3]Dept Neurosci & Cell Biol/ Pediatrics (Child Neurol. & Neurodevelopmental Disa, [1]Rutgers Robert Wood Johnson Med. Sch., Piscataway, NJ; [4]Univ. of Maryland, Baltimore County, Baltimore, MD; [5]Neurosci. and Cell Biol., Rutgers Univ., Piscataway, NJ

Abstract: Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by deficits in social interaction and presence of restricted, repetitive behaviors. While there is vast clinical and genetic heterogeneity among individuals with ASD, the neurobiological distinctions between ASD subtypes are largely unknown. To begin addressing this issue, we are comparing neurodevelopmental abnormalities in idiopathic autism (I-ASD) to genetically defined, 16p11.2 deletion subtype (16p-ASD). For our studies, we have generated induced pluripotent stem cells (iPSCs) from 8 individuals with I-ASD and from 3 patients with ASD and 16p11.2 deletion. I-ASD patients were derived from an 85 NJ family cohort recruited by collaborator L Brzustowicz, while 16p-ASD individuals derive from the Simons VIP cohort. We generated neural precursor cells (NPCs) from both sets of iPSCs and hypothesize that 16p-ASD NPCs may exhibit neurobiological features, such as neurite outgrowth, that differ from I-ASD NPCs. To quantify neurite outgrowth, NPCs were plated at low density under stimulation of developmentally relevant extracellular factors (EFs), fixed at 48h, and analyzed for % of cells with neurites. EFs include: pituitary adenylate cyclase-activating peptide (PACAP), fibroblast growth factor (FGF), and serotonin (5HT).
Control (Con) NPCs derived from 3 unaffected, age-matched individuals showed increased neurite outgrowth under stimulation of PACAP and 5HT, whereas FGF reduced neurite outgrowth. Interestingly, 16p-ASD NPCs were phenotypically more similar to Con than to I-ASD NPCs: while 2 I-ASD individuals were unresponsive to PACAP, 16p-ASD NPCs had PACAP stimulated neurite outgrowth similar to Con NPCs; similarly, FGF reduced neurites in

Con and 16p-ASD NPCs but led to increased neurites in I-ASD. These findings suggest there are neurobiological differences between I-ASD and 16p-ASD subtypes under EF stimulation. Interestingly, however, subgroup heterogeneity of ASD was also suggested by NPCs responses to 5HT. While 2 I-ASD patients did not respond to 5HT, 1 16p patient (with milder ASD) showed 5HT stimulated neurite increase while the other 16p patient (with severe ASD) failed to respond. Thus, while ASD subtype specific phenotypes are observed, in some cases, patient-specific phenotypes are present and may correlate with clinical symptom severity. In sum, our studies suggest there may be ASD subtype-specific differential responses between I-ASD and 16p-ASD to EFs, leading to distinct neurobiological phenotypes. By defining distinct phenotypes and mediating signaling pathways, we may ultimately design patient-specific therapeutic interventions.

Disclosures: C.C. Peng: None. **S. Prem:** None. **R.J. Connacher:** None. **M. Hale:** None. **J.H. Millonig:** None. **E.M. DiCicco-Bloom:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.05/B47

Topic: A.03. Stem Cells and Reprogramming

Support: P30 DK020595

Title: Analysis of neuronal development in patients with KCNJ11/Kir6.2 mutations

Authors: *G. DALGIN[1], A. J. GARCIA, III[2], S. A. W. GREELEY[3], L. H. PHILIPSON[1], G. I. BELL[1]
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Abstract: Gain of function mutations in the ATP-sensitive potassium (K_{ATP}) channel gene *KCNJ11/Kir6.2* are the most common genetic cause a of permanent neonatal diabetes mellitus (PNDM). *KCNJ11* function is necessary in multiple cell types, for example in beta cells and neurons, and mutations cause pleiotropic phenotype. In addition to diabetes, *KCNJ11* patients exhibit neuropsychological dysfunction and neurodevelopmental defects. Sulfonylrea (SU) treatment closes mutant K_{ATP} channel and provides a better glycemic control and improves neurological function in *KCNJ11* patients. Our studies demonstrated that patients benefited from earlier SU administration and needed lower doses to control hyperglycemia. Studies from murine models and our behavioral, neuropsychological and clinical data from our patients suggested that neurological disorders are independent of defects in beta-cell function. We hypothesize that the underlying cause of neurological disorders in *KCNJ11* patients is due to effect of p.KCNJ11 on neuronal development. We decided to analyze the cause of the neurodevelopmental defects by

differentiating neurons *in vitro* from patient-derived human induced pluripotent stem cells (hiPSCs). We reprogramed hiPSCs from three *KCNJ11* patients exhibiting mild to severe forms of neurological impairments, R201H, R201C and V59M respectively. We are currently differentiating forebrain type of neurons in monolayer and 3D conditions. We will perform cellular and molecular analysis to compare *KCNJ11*-mutant hiPSCs derived neurons to age and sex match controls. We predict that patient derived neurons will exhibit neurodevelopmental defects in culture and may suggest that neurological defects observed in patients are due to impaired neural developmental.

Disclosures: G. Dalgin: None. **A.J. Garcia:** None. **S.A.W. Greeley:** None. **L.H. Philipson:** None. **G.I. Bell:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: A.03. Stem Cells and Reprogramming

Support: NJ Governor's Council for Autism Research

Nancy Lurie Marks Family Foundation

Title: Idiopathic autism neural precursor cells exhibit differential sensitivity to environmental factor treatment

Authors: *M. WILLIAMS[1], C. PINTO[2], S. PREM[4], X. ZHOU[3], P. MATTESON[3], J. H. MILLONIG[3], E. M. DICICCO-BLOOM[5]
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by abnormalities in social interactions and stereotyped/restrictive behavior. Though the role of genetic abnormalities in ASD pathogenesis is well accepted, contributions of environmental factors are less well defined. It is hypothesized that greater ASD genetic vulnerability in conjunction with early developmental exposure to environmental toxicants may cause some children to cross biological and/or behavioral thresholds into ASD. Study of ASD has been hindered by disease heterogeneity and difficulties in creating representative mouse models. To study deficits in idiopathic ASD, we generated induced pluripotent stem cell lines from 8 severely affected males and their unaffected brothers (Sib) and derived neural precursor cells

(NPCs). By applying environmental factors such as methylmercury (MeHg) and hydrogen peroxide (H_2O_2) we can investigate gene by environment interactions and how stressors may impact biological processes relevant to ASD pathology, such as proliferation or reactive oxygen species (ROS) production.
To define effects, NPCs were grown at high density (50K cells/cm^2) and incubated without or with either MeHg or H_2O_2 and were labeled at 48h with tritiated thymidine to assess DNA synthesis. In parallel, sister cultures were dissociated to quantify live cell numbers via hemocytometer. To examine ROS, cells cultured in 96-well plates were incubated for the last hour with ROS indicator DCFH-DA, and Hoechst stain, and analyzed using fluorescent microplate reader, with ROS values normalized to cell number. For each person (ASD, Sib) we compared 2-3 independent iPSC clones.
Interestingly, in preliminary results examining MeHg (0.01-1µM), ASD NPCs from 2 families were less sensitive to adverse effects on proliferation in comparison to Sib control. After 48h MeHg exposure, Sib NPCs exhibited a 70% reduction in DNA synthesis whereas ASD NPCs exhibited a 40% reduction. This reduction in DNA synthesis was accompanied by similar loss in cell numbers. Using a 2nd environmental factor, H_2O_2 (0.01-.2 mM), yielded comparable results. Furthermore, in examining ROS production, preliminary results suggest that ASD NPCs exhibit a ~50% increase in baseline ROS and differential responses to challenge with H_2O_2.
In aggregate, our observations suggest we are able to discover differences in responses to environmental factors, MeHg and H_2O_2, in ASD-implicated biological processes. In examining 2 ASD-Sib pairs, our toolset has begun to uncover patient-specific differences in cellular phenotypes and their response to environmental factors.

Disclosures: **M. Williams:** None. **C. Pinto:** None. **S. Prem:** None. **X. Zhou:** None. **P. Matteson:** None. **J.H. Millonig:** None. **E.M. DiCicco-Bloom:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

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Topic: A.03. Stem Cells and Reprogramming

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CIRM DISC2-09032

NINDS R24 201603716

NINDS 1R01NS102486-01

Title: CRISPR-dCas9-mediated induced neurons for patient-specific disease modeling

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Abstract: Disorders of the central nervous system (CNS) result in one of the largest economic burdens on society. While research has made enormous contributions in the identification of CNS disease-related genes, the underlying molecular mechanism associated with disease pathology in human neuronal cells remain unclear. Therefore, developing a method to recapitulate disease- and age-associated phenotypes in human neurons grown *ex vivo* is critical for therapeutic development and furthering understanding on CNS disorders. Emerging research suggests that upregulation of endogenous “neuronal-fate” determining genes using CRISPR guide RNAs (gRNA) with a nuclease-deficient Cas9 (dCas9) fused with a transcriptional activator, can transdifferentiate somatic cells to functional induced neurons (iN). To study a rare infantile epileptic disorder as well as juvenile and adult onset Huntington’s disease we will use CRISPR-dCas9 fused to an activator domain to reprogram patient lymphoblasts and fibroblasts to iN, respectively. iN cellular reprogramming, facilitated by CRISPR-dCas9 transcriptional activation, will be characterized by qPCR to quantify gene expression of targeted neuronal-fate determining and downregulated cell source genes, and immunocytochemistry to label immature, developing, and mature neuronal surface markers. iN derived from patient and healthy aged-matched lymphoblasts and fibroblasts will be compared morphologically to confirm disease- and age-associated phenotypes in patient-specific iNs. Patient lymphoblasts and fibroblasts that have been transdifferentiated, labeled with neuronal markers and analyzed for disease- and age-associated phenotypes will then be used to study disease pathology in an induced neuron. Induced neurons generated from patient fibroblasts and lymphoblasts will create an efficient disease model for investigators studying the molecular mechanisms of central nervous system disorders.

Disclosures: J.L. Carter: None. **P. Deng:** None. **J. Halmai:** None. **J. Nolta:** None. **D. Segal:** None. **K. Fink:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.08/B50

Topic: A.03. Stem Cells and Reprogramming

Title: *In vitro* disease modeling for sleep bruxism using induced pluripotent stem cells

Authors: *Y. TOZAWA[1], N. KENTO[1], K. YONEIMA[1], T. MATSUMOTO[1], Y. ABE[1], K. IMAIZUMI[3], K. MISHIMA[2], J. TANAKA[2], W. AKAMATSU[4], H. OKANO[3], K. BABA[1]
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Abstract: Sleep bruxism (SB) is classified as a sleep-related movement disorder characterized by grinding and clenching of the teeth during sleep. The mechanical stress of SB is associated with poor prognosis of dental treatment and seriously compromises patients' quality of life. Although there is a consensus that several source of causative factors are involved, little is known about the etiology of SB. In addition, molecular mechanisms contributing to SB has never been investigated. Our previous study found a significant association between SB and single nucleotide polymorphism (SNP) of serotonin 2A receptor (*HTR2A*) gene (rs6313 C>T), which suggested C allele carrier is associated with a 4.25-fold increased risk of SB, however; the effects of the SB-associated variant on the function of the serotonergic neuron have not been investigated, mainly because of the limited accessibility to the brain. Based on this finding, the aim of this study was to establish SB disease model using the *HTR2A* expressing neurons derived from patient-specific pluripotent stem cells (iPSCs).
Two SB patients with C/C genotype of rs6313 and two controls with T/T genotype were screened by laboratory-based polysomnographic recordings and the TaqMan genotyping assay. iPSCs were generated from monocytes in peripheral blood samples of two SB patients and two controls by transducing episomal plasmids encoding transcription factors and three iPSC clones were isolated from each individual. The established iPSCs were differentiated into serotonergic neurons using the neurosphere culture system. Successful differentiations of these iPSC lines to serotonergic neurons were confirmed by immunostaining. In addition, expression levels of *HTR2A* gene of these neurons, as evaluated by qPCR, were much higher than those of T cells raised from the original peripheral mononuclear cells.
The successful generation of *HTR2A* expressing neural cells from SB patient-specific iPSCs allows us to examine the physiological effects of SB-associated genetic variation, which might elucidate the etiology and underlying mechanism of SB. In addition, this method can be applied to other types of diseases that are associated with *HTR2A gene* polymorphisms.

Disclosures: Y. Tozawa: None. **N. Kento:** None. **K. Yoneima:** None. **T. Matsumoto:** None. **Y. Abe:** None. **K. Imaizumi:** None. **K. Mishima:** None. **J. Tanaka:** None. **W. Akamatsu:** None. **H. Okano:** None. **K. Baba:** None.

Poster

032. iPSCs: Disease Models

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Program#/Poster#: 032.09/B51

Topic: A.03. Stem Cells and Reprogramming

Support: FAPESP Grant 2015/24001-1

CNPq Grant 447949/2014-4

Title: Epigenetics regulation on Ciliary Epithelium stem cells during retinal degeneration

Authors: *C. B. DEL DEBBIO, R. C. T. RODRIGUES
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Abstract: The retina is an essential structure for sensory perception in vertebrates and is susceptible to various environmental and genetic degenerative insults that results in visual loss or blindness. Despite the absence of efficient regenerative mechanisms, some epithelial cells located in the peripheral retina of mammalians, in the Ciliary Epithelium (CE) region, were identified as progenitor/stem cells with the capacity to generate retinal neurons. Although CE cells has presented retinal regenerative capacity, this ability is not developed properly due to the presence of inhibitory mechanisms acting on the regenerative potential of these cells. It is known that some epigenetic factors have influenced the cell reprogramming of stem and iPS cells and, for that reason, we evaluate the expression profile of DNA methyltransferase (DNMT), histone acetyltransferases (HATs), histone deacetylases (HDACs) and microRNAs (miRNAs), in CE cells from normal animals and retinal degeneration model. CE cells from normal animals (Sprague Dawley-SD) and retinal degeneration models (P23H) were collected from different animal ages and retinal degeneration stages (before, during and after retinal degeneration starts). Transcriptional expression of *dnmts (1, 3a* and *3b)*, *hat1* and *hdac (1, 2, 3, 4* and *5*), as well as miRNA expression were analyzed. Our results indicated that *dnmts 1* and *3a* expression were decreased in P23H animals in comparison to SDs (30% and 20%, respectively). No differences were observed in *dnmt3b* and *hat1* transcriptional expression. Likewise, all *hdac* investigated decreased expression in CE cells from animals with retinal degeneration in comparison to controls (*hdac1*=20%, *hdac2*=12%, *hdac3*=20%, *hdac4*=14% and *hdac5*=21% decreased). Furthermore, mature miRNA expression analysis by microarray, indicated higher rates of miRNA expressed in CE cells incapable to become reprogrammed as stem/progenitor cells in the presence of growth factors, in comparison to those that are able to be reprogrammed (120 and 32 miRNAs, respectively). Our results suggest that the loss of cells during retinal degeneration decreased the expression of important epigenetics mechanisms involved in stem cells activation and differentiation. In the meantime, miRNAs, known to prevent some target protein expression, were increased in CE cells that are unable to be reprogrammed as stem/progenitor cells. The information gleaned from this study may provide valuable insight into the cellular and molecular events that underlie the reprogramming response of CE cells and the mechanism of retinal recovery.

Disclosures: C.B. Del Debbio: None. **R.C.T. Rodrigues:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.10/B52

Topic: A.03. Stem Cells and Reprogramming

Support: Commerical

Title: Utilizing CRISPR/Cas9 genome editing in differentiating human induced pluripotent stem cells as a functional genomics approach to study neurodegenerative disease

Authors: *J. DIZON, E. WILLEMS, T. GOKIRMAK, R. VEGA, R. LACAMBACAL, X. LIANG, C. REVANKAR, K. KIMLER, D. PIPER
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Abstract: Induced pluripotent stem cells (iPSCs) can be differentiated into numerous cell types and provide useful tools to create translatable neuronal assay systems, effective for both *in vitro* disease modeling and drug discovery efforts. The advent of CRISPR/Cas9 genome editing platforms has expanded methods to study genetic defects in disease by enabling the introduction of genetic changes in iPSCs, which can subsequently be differentiated to the affected cell type. Although CRISPR/Cas9 mediated genome editing in iPSCs is the optimal approach to study disease-specific genetic defects, genome editing during or after differentiation may also support high-throughput functional genomics screens to understand the biology of neuronal development or to identify novel targets associated with a particular disease. To facilitate CRISPR/Cas9 mediated editing during neuronal differentiation, we generated an iPSC line that stably expresses the Cas9 nuclease protein. We then derived several neuronal progenitor lines from the Cas9 iPSCs, including floor plate progenitors, which support the high purity generation of dopaminergic neurons, and neural stem cells, which can be differentiated into cortical neurons and other neural cell types (including glia). Here we demonstrate the ability to use our CRISPR tools to edit the genome efficiently in these Cas9 expressing neuronal progenitor cells and suggest that this approach will support high-throughput functional genomic screens in disease-relevant neuronal models. Furthermore, we developed a series of high content imaging assays specifically for neuronal cell types to study disease-relevant cellular phenotypes in neuronal progenitors or neuronal cells derived from pairs of iPSCs that have been edited to contain both wild-type and common disease causing genetic backgrounds. Using the described methods, iPSC-derived neurons can be tested for cell health and viability, neurite outgrowth, synaptogenesis and protein aggregation. These assays provide important tools for measuring phenotypes commonly seen in neurodegenerative diseases. By combining the genome editing of progenitors with these disease-relevant high-content imaging assays and cellular models, we have built a system that enables the identification of novel genetic targets to discover new

therapies for neurobiological diseases. We thus provide a series of tools that can be used to develop and implement high-throughput *in vitro* neuronal assays that are amenable to both drug-screening and functional genomics platforms. Such assays would not only be relevant for the neuronal models shown here, but translate across the neurobiological disease space.

Disclosures: **J. Dizon:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **E. Willems:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **T. Gokirmak:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **R. Vega:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **R. Lacambacal:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **X. Liang:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **C. Revankar:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **K. Kimler:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **D. Piper:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.11/B53

Topic: A.03. Stem Cells and Reprogramming

Support: National Science Foundation of China (81371384)

Special fund for experimental animals of Sshanxi Province[2014(06)] and [2014(k15)]

Title: miR-126 expression at different segments after spinal cord injury

Authors: *C. WANG, X. LI, Y. ZHANG, F. TIAN, M. FU, P. LI
Shanxi Med. Univ., Shanxi, China

Abstract: The microRNA miR-126 plays an important role in vascular development and apoptosis and is involved in differentiation of neural stem cells. Our pilot studies revealed that miR-126 expression is higher in motor neurons than neural stem cells, suggesting that miR-126 may be involved in motor neuron differentiation as well as repair of spinal cord injury (SCI). In the current study, we induced mouse SCI using Allen's contusion model, then examined the expression of miR-126 using qRT-PCR and assessed inflammation as well as tissue and cell pathology using H&E and Nissl staining in the area of direct injury (centered around thoracic segment T10) as well as the segments 0.5cm cervical and 0.5 cm sacral to the region of direct mechanical trauma. We observed that miR-126 expression was lowest in the contusion area, gradually increased with time, reaching a peak at 28d. Cervical to the area of injury, miR-126 expression was higher than the contusion area, and peaked at 7d. Sacral to the area of injury,

miR-126 expression showed a complex, biphasic response with a minimum at 3d, up-regulation at 7d and 14d, down-regulation at 21d, and a peak at 28d after SCI. At 1d after SCI, severe congestion and edema was observed at the site of contusion but not in the segments cervical and sacral to the injury site. However, at 3d, we observed severe edema and cell loss around the area of injury and edema in the segments cervical and sacral to the area of injury. The edema in all three segments subsided by 7d. Interestingly, at 21d after SCI, greater numbers of cells were observed at the contusion area, despite the presence of a necrotic cavity. This cavity increased in size by 28d after SCI, but there was no additional increase in cell numbers. Our results showed that edema was the most severe at 3d, a time point at which the expression of miR-126 was lowest. By 7d post-contusion, both edema and inflammation subsided and the expression of miR-126 in the area of injury was still very low, whereas miR-126 expression in the segment cervical to the injury peaked. This suggests that the increased expression of miR-126 at this segment may play an important role in regulating the anti-inflammatory effect. At 14d, the regeneration of nerve cells was observed, functional recovery was most obvious, and the expression of miR-126 was higher in the segment sacral to the injury site, indicating that the promotion of nerve cell regeneration and functional improvement could be regulated by the miR-126. In conclusion, we observed a correlation between the time course of miR-126 expression, inflammation, neurogenesis, and functional recovery. These data suggest that miR-126 may play an important role in recovery after SCI.

Disclosures: **C. Wang:** None. **X. Li:** None. **Y. Zhang:** None. **F. Tian:** None. **M. Fu:** None. **P. Li:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.12/B54

Topic: A.03. Stem Cells and Reprogramming

Support: Angelman Syndrome Foundation

Dup15q Alliance

NIH Grant MH094896

CT Regenerative Medicine Research Fund

Title: Hyperexcitability in stem cell-derived neurons from patients with chromosome 15q-associated neurodevelopmental disorders

Authors: *J. J. FINK, J. D. SCHREINER, E. S. LEVINE
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Abstract: Deletions and duplications of chromosome 15q11-q13 leads to Angelman syndrome (AS) and chromosome 15q duplication syndrome (Dup15q), respectively. Though they are due to opposite genetic changes, patients with these clinically distinct syndromes share a variety of phenotypes including language/speech impairments, motor abnormalities, and developmental delay. Interestingly, >50% of patients with either AS or Dup15q suffer from some form of seizure disorder. Additionally, a large percentage of Dup15q patients also meet the diagnostic criteria for autism spectrum disorder. The causative gene of Angelman syndrome has been identified as UBE3A, which encodes for an E3 ubiquitin ligase protein responsible for tagging its targets for degradation by the proteasome. The causative gene(s) for Dup15q are less clear, but UBE3A is thought to play an important role. In both cases, evidence from mouse models of these disorders suggests that synaptic impairments may be a large contributor to the cellular pathophysiology of these syndromes, however there is still very little insight into the cellular mechanisms that may account for the high prevalence of seizures in these patients.
We have previously identified a robust cellular phenotype in Angelman syndrome neurons using patient-specific induced pluripotent stem cell (iPSC) lines with electrophysiology and population calcium imaging. The phenotype of AS iPSC-derived neurons includes a depolarized resting membrane potential (RMP) and impairments in synaptic signaling and plasticity, compared to controls. Interestingly, a depolarized RMP with no change in action potential (AP) threshold suggests a mechanism for hyperexcitability in AS-derived neurons. Given the close relationship of AS and Dup15q and the shared involvement of UBE3A, we examined the development of these same features in neurons derived from Dup15q patients. Surprisingly, we find that these properties remain largely normal in Dup15q neurons, suggesting that changes in RMP are not a phenotype of neurodevelopmental disorders in general. Instead, neurons derived from Dup15q patients have a hyperexcitability phenotype that develops after 20 weeks in culture and includes significantly elevated spontaneous AP firing and a higher degree of synchronous activity. Additionally, these neurons have impaired homeostatic synaptic plasticity compared to control neurons. Overall, these distinct cellular phenotypes may prove useful for identifying novel targets for drug discovery and for screening potential therapeutics aimed at reversing the seizures and other symptoms associated with Angelman syndrome and Dup15q.

Disclosures: **J.J. Fink:** None. **J.D. Schreiner:** None. **E.S. Levine:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

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Program#/Poster#: 032.13/B55

Topic: A.03. Stem Cells and Reprogramming

Support: CRM fellowship FP00087081

Title: A novel human iPSC-based 3D culture system for studying APOE isoform-dependent pathways in Alzheimer's disease

Authors: *J. ZHAO, M. DAVIS, C. LIU, G. BU
neuroscience, Mayo Clin., Jacksonville, FL

Abstract: Apolipoprotein E4 (*APOE4*) is the strongest genetic risk factor for late-onset Alzheimer's disease (AD) compared to the common *APOE3* allele. In the central nervous system, apoE is primarily produced by astrocytes and transports lipids to neurons to support synaptic functions and injury repair. Compared to animal models, human induced pluripotent stem cells (iPSCs) derived from individuals carrying specific gene variants or mutations provide an attractive cellular model upon differentiation into specific cell types to study disease mechanisms more relevant to humans. We have recently successfully differentiated human iPSCs derived from cognitively normal individuals carrying *APOE3/3* or *APOE4/4* genotype into mature astrocytes, and confirmed that these human astrocytes secrete abundant lipidated apoE that can support neuronal homeostasis. In addition, *APOE4/4* astrocytes are associated with significantly less cholesterol compared with *APOE3/3* astrocytes. To further understand how human apoE isoforms from astrocytes differentially regulate neuronal functions in a system that more accurately represents the *in vivo* environment, we established a novel three-dimensional (3D) culture system using human iPSC-derived neurons and astrocytes with different apoE isoforms. Co-culture of human iPSC-derived neurons and astrocytes in suspension led to the formation of 3D spheroids which expressed various cell type-specific markers. More importantly, we found that human iPSC-derived astrocytes promoted neuronal maturation and synaptogenesis in the 3D culture system in an *APOE* genotype-dependent manner. Thus, our human iPSC-based 3D culture model provides a novel platform to study disease-related pathways in a physiologically relevant enviorment. Using such models, we can gain better understanding of apoE isoform-dependent effects in AD-related pathways, informing new targeting strategies for therapy.

Disclosures: J. Zhao: None. **M. Davis:** None. **C. Liu:** None. **G. Bu:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

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Program#/Poster#: 032.14/B56

Topic: A.03. Stem Cells and Reprogramming

Support: The Farber Family Foundation

The Margaret Q. Landenberger Research Foundation

The Strauss Foundation

Title: Characterization of iPSC-derived skeletal muscle and motor neurons in an *In vitro* model of the neuromuscular junction

Authors: *B. A. MORRIS[1,2], S. BONANNO[2], E. KROPF[3], B. K. JENSEN[2], L. M. IACOVITTI[3], D. TROTTI[2], P. PASINELLI[2]
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Abstract: It is commonly accepted that one of the hallmarks of Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disease characterized by the loss of both upper and lower motor neurons, is a "dying-back" phenotype. Specifically, it has been established that degeneration of the distal axon at the neuromuscular junction (NMJ) and subsequent muscle denervation is an early pathogenic hallmark in ALS. This observed denervation results in muscle atrophy. Accordingly, identifying ALS-specific abnormalities at the NMJ creates avenues for therapeutic intervention. Using small molecule induction protocols, we have differentiated human skeletal muscle and human motor neurons from induced pluripotent stem cells (iPSCs). The human skeletal muscle is positive for the mature muscle marker desmin and exhibits spontaneous twitching that is sustained from 36 days post-induction onward. The human motor neurons are both ChAT-and HB9-positive. Preliminary gene expression profiles confirm complete differentiation and maturation into skeletal muscles and spinal motor neurons respectively. Our goal is to create patient-derived *in vitro* NMJ models using a microfluidic-chamber system that permits individual manipulation of each cell type based on spatial separation. This will allow for the study of NMJ formation, denervation, and dysfunction using an individualized, patient-based approach. Ultimately, we aim to identify NMJ-specific molecular targets for therapeutic intervention aimed at stabilizing motor neuron-muscle connectivity in ALS.

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Poster

032. iPSCs: Disease Models

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Program#/Poster#: 032.15/B57

Topic: A.03. Stem Cells and Reprogramming

Support: NIH U19 Grant MH106434

Title: Astrocytes derived from induced pluripotent cells from bipolar disorder patients

Authors: *C. DELONG[1,2], A. WILLIAMS[2], E. MARTINEZ[2], M. BAME[2], G. MURPHY[3], M. MCINNIS[2], K. O'SHEA[1,2]
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Abstract: The role of astrocytes in mood disorders has been a subject of interest in recent years, with evidence that supports involvement of several different areas of astrocyte biology, including mitochondrial dysfunction and aberrant glutamate transport. Mitochondrial morphology and function in bipolar disorder (BP) was examined in astrocytes differentiated from patient-derived induced pluripotent stem cells (iPSC) from 3 BP and 3 control individuals. The iPSC lines were differentiated into neural precursors via dual SMAD inhibition, followed by a 70-day incubation in medium containing N2, fibroblast growth factor-2 (FGF-2), and epidermal growth factor (EGF) in suspension (astrospheres) followed by dissociation into astrocyte monolayer cultures (adapted from Krencik and Zhang, 2011). Passaging and expansion in FGF-2 and EGF resulted in a population of which up to 99% were positive for the glial precursor marker CD44. Electron microscopy revealed that mitochondria in BP astrocytes were morphologically different than in control astrocytes, displaying decreased perimeter, length, axis ratio, and complexity, and increased circularity. Comparison of mitochondrial membrane potential (MMP) using flow cytometric analysis of JC-1 uptake into mitochondria revealed a 30% higher MMP in BP astrocytes compared to controls. Because mitochondrial hyperpolarization can lead to higher levels of reactive oxygen species (ROS), oxidative stress, and cell death, future investigations will measure ROS and effects on neuronal survival in coculture. Since RNA-Seq analysis of astrocytes derived from BP vs controls revealed decreased expression of genes involved in glutamate transport and signaling, including EAAT1, EAAT2, and GRM3, we will also look at glutamate uptake and calcium signaling, as well as synaptic markers in astrocyte-neuron cocultures. Our results are in agreement with the ideas of mitochondrial dysfunction and disturbance of the glutamatergic system in BP.

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Poster

032. iPSCs: Disease Models

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Topic: A.03. Stem Cells and Reprogramming

Support: Hussman Foundation Pilot Grant HIAS15004

Title: A 3-D human induced pluripotent stem cell model of autistic spectrum disorder as a functional analysis platform

Authors: *A. W. PHILLIPS, J. NESTOR, M. NESTOR
Hussman Inst. for Autism, Baltimore, MD

Abstract: Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with a wide spectrum of phenotypes, and marked qualitative differences in social interaction, communication, and behavior. Development of neurobiological diagnosis and treatment protocols is impeded by a lack of effective model systems to determine pathobiology. 3-dimensional (3-D) cultures generated from ASD patient-derived iPSCs (hiPSCs) provide a platform to functionally evaluate neural circuits.. Whole-genome sequencing studies of the hiPSC lines identified in this cohort contain mutations and other irregularities in genes that may affect components of the cytoskeleton and its integrity (Cukier et al., 2014). One characteristic of ASD is an apparent excitatory-inhibitory imbalance, possibly due to dysfunctional cytoskeletal rearrangement leading to altered GABAergic neuronal function. This is important because many of the genes identified in autism are related to pathways involving cell adhesion, cytoskeletal integrity, and cell motility.
Objective: We interrogated a 3-D serum free embryoid body (SFEB) model based on Nestor et al., 2013 with respect to circuit function and the cytoskeleton. Multi-electrode array recordings (MEA) on SFEBs were used to assess the role of various ASD-related variants in our cohort of 7 individuals with idiopathic autism. Additionally we assayed stress fiber formation, endocytosis and ligand internalization in SFEBs to evaluate cytoskeletal function.
Methods: 3-D SFEB cultures were generated by plating 2-4 x 10^4 cells into a low adhesion V-bottomed 96-well plate for 14 days then switched to 0.4µm cell culture inserts for the duration of the culture. SFEBs were plated onto PEI/ laminin treated 48 well MEA plates and recordings taken at days 30, 90 and 120 to determine spontaneous spiking across networks of neurons. 3-D cultures were prepared for phalloidin staining to visualize actin fibers and immunochemistry used to identify interacting proteins with the actin-myosin complex. Cells were then evaluated for their ability to incorporate labeled vesicles for endocytosis and labeled molecules for pinocytosis.
Results: Our analysis revealed an increase in SFEB spiking activity that peaked at day 90. Further, studies revealed stress fiber activity that increased with culture age. In addition, the downstream impact of potentially impaired cytoskeleton in our ASD cohort showed different pinocytosis turnover rates of pHrodo-green dextran.
Conclusion: These data demonstrate the utility of the 3-D *in vitro* platform as a tool in understanding the functional impact of genes in our cohort on the cellular activity of developing neurons.

Disclosures: A.W. Phillips: None. **J. Nestor:** None. **M. Nestor:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.17/B59

Topic: A.03. Stem Cells and Reprogramming

Title: Novel tools support the efficient derivation of clonal CRISPR/Cas9 edited human induced pluripotent stem cells to construct models of neurodegenerative diseases

Authors: *R. E. LACAMBACAL[1], E. WILLEMS[2], T. GOKIRMAK[2], J. DIZON[2], C. REVANKAR[2], R. VEGA[2], K. KIMLER[2], X. LIANG[2], R. NEWMAN[3], D. KUNINGER[3], D. PIPER[2]
[2]Cell Biol. R&D, [1]Thermo Fisher Scientific, Carlsbad, CA; [3]Cell Biol. R&D, Thermo Fisher Scientific, Frederick, MD

Abstract: Induced pluripotent stem cells (iPSCs) have been globally recognized as a multipurpose research tool for modeling diseases, developing and screening potential drugs, and implementing cell transplantation therapies to support regenerative medicine. The ability to differentiate human iPSCs into any cell type, including dopaminergic neurons, supports the study of neurological diseases *in vitro*. The emergence of genome editing tools, such as the CRISPR/Cas9 system, allow diseases to be modeled at the genetic level and studied at the cellular level. However, genetic mimicking of disease has been difficult due to challenges in the implementation of genome editing tools in iPSC, particularly issues associated with tool delivery, cell recovery and clonal isolation of genome-edited cells. Here, we describe a workflow that facilitates the generation and isolation of clonal CRISPR-edited iPSCs through the use of a novel toolset. We observed high genome editing efficiency using an iPSC line that stably expresses the Cas9 protein and obtained improved survival of the iPSCs after delivery of the editing tools through culture in StemFlex™ medium, a novel PSC culture system. Furthermore, we have demonstrated that single edited iPSCs can be isolated through the combination of an optimized cell sorting method and expanded as single cell clones with reagents that support single cell survival. Through this workflow we have generated several iPSC lines carrying SNP mutations relevant to Parkinson's disease. Dopaminergic neurons were generated from these lines and possible phenotypic defects were studied. In summary, we describe a genome editing platform that can reliably produce clonal gene-edited iPSCs that can be used as cellular models to study neurodegenerative disease phenotypes *in vitro*. This gene editing workflow can be used to mimic these human diseases, and will support significant insights into neurodegenerative diseases at the genetic and cellular levels.

Disclosures: **R.E. Lacambacal:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **E. Willems:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **T.**

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Poster

032. iPSCs: Disease Models

Location: Halls A-C

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Topic: A.03. Stem Cells and Reprogramming

Support: NJ Governor's Council for Autism Research

Nancy Lurie Marks Family Foundation

Title: Gene expression analysis of idiopathic autism iPSCs and NSCs

Authors: *M. MEHTA[1,2], P. G. MATTESON[2], E. DICICCO-BLOOM[1], J. H. MILLONIG[1,2]
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Abstract: The heterogeneity of autism, encompassing genetic, epigenetic and environmental factors make it a difficult disorder to study. Advances in stem cells have made it possible to reprogram somatic cells into iPSCs, allowing for the potential to model human diseases in vitro. For the present study, blood samples were collected from sex-matched sibling pairs, one with autism and one normal sibling control; to reduce potential heterogeneity of samples, 8 families were selected for autism plus another language disorder called Specific Language Impairment. T cells were then reprogramed into iPSCs and differentiated into neural stem cells (NSCs). 3 clones from each individual were picked to serve as biological replicates. Three families have been analyzed thoroughly and robust autism-specific phenotypic differences have been reported for proliferation, neurite extension and migration. Gene expression analysis was then performed on the same families, using a 23 gene multiplex Luminex assay for NSC expressed genes. In one family a measurable upregulation in gene expression for the affected individual compared to the unaffected individual was observed in iPSCs for Pax6, Msi1, Metrn, Sox2 and Sox1 ($p < 0.05$). Gene expression analysis using the same 23 gene assay is currently being completed for both iPSCs and NSCs for all three families and significant changes have been observed. In addition,

gene expression analyses are also being conducted on a separate set of families focusing on a Chromosome 16 CNV deletion, 16p11.2, which increases risk for autism. A separate Luminex panel has been employed to measure the expression of the 27 deleted genes, in iPSCs and NSCs. Significant differences in gene expression have been observed in one family thus far, and these results are now being replicated to include additional pairs of families. Overall, this methodology allows for a more personalized approach for studying idiopathic autism, and may provide insight into how aberrant gene expression contributes to the autism-specific proliferation and differentiation phenotypes. This research is supported through a grant from NJ Governor's Council for Autism Research and Nancy Lurie Marks Family Foundation.

Disclosures: M. Mehta: None. **P.G. Matteson:** None. **E. DiCicco-Bloom:** None. **J.H. Millonig:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.19/B61

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant NS083009 to DKOD

Title: Generation of isogenic knock-in iPSCs to evaluate cellular mechanisms of SCN1A epilepsies: GEFS+ (R1648H) and DS (R1648C)

Authors: *C. HAWKINS, O. SAFRINA, N. OSMAN, D. K. O'DOWD
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Abstract: Epilepsy is a heterogeneous disorder classified by recurrent seizures due to periods of hyperexcitability in the nervous system. Voltage-gated ion channels regulate excitability in both excitatory and inhibitory neurons. Over 1200 mutations have been identified in one particular voltage-gated sodium channel, NaV1.1, whose alpha subunit is coded by the gene SCN1A. One mutation, R1648H, was found in a family with genetic epilepsy with febrile seizures Plus (GEFS+), a disorder characterized by febrile or heat induced seizures early in life that persist beyond 6 years of age. Another mutation at the same position, R1648C, was identified in a patient with Dravet Syndrome (DS), a more severe form of epilepsy that also starts early in life with febrile seizures but often entails other co-morbidities including cognitive impairment. While patient-derived induced pluripotent stem cell (iPSC) lines are a valuable model for studying genetic epilepsies, it is difficult to clearly identify mutation induced changes by comparing between cell lines, even from siblings, due to differences in genetic background. To create isogenic lines we used the CRISPR/Cas9 gene editing strategy. A control cell line from an unaffected individual was transfected with a plasmid containing the guide RNA (gRNA) to target

the genome, Cas9 for introducing a double-stranded break, and puromycin marker for selection, as well as a separate repair template containing the R1648C mutation for homology directed repair. The mutation site was 16bp from the Cas9 cutsite. Of the 79 colonies that were manually isolated after puromycin selection, 15% were heterozygous and none were homozygous for the R1648C mutation. Ten of the 12 heterozygous clones had a series of double-peaks after Cas9 cut site, reflecting sequence difference in the two alleles, but two of the clones did not have any other amino acid altering mutations, giving a final efficiency of 2.5%. Currently, the same strategy is being used to generate an R1648H hiPSC line. Before differentiating into neurons the R1648H and the R1648C iPSC lines will be expanded and karyotyped. One clonal line with each mutation, along with the control line, will be differentiated into neurons and the firing properties and sodium currents will be evaluated. The effects of two mutations at the same position that lead to GEFS+ or DS in an isogenic background will provide insight into underlying mechanisms contributing to the large differences between these two disorders.

Disclosures: C. Hawkins: None. **O. Safrina:** None. **N. Osman:** None. **D.K. O'Dowd:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

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Program#/Poster#: 032.20/B62

Topic: A.03. Stem Cells and Reprogramming

Support: The Blazer Foundation

NIH Grant R21NS089042

Title: Modelling hereditary spastic paraplegia type 5 using human induced pluripotent stem cells

Authors: *G. NANDI[1], Y. MOU[1], J. E. NIELSEN[2], C. CRISCUOLO[3], M. J. FRAIDAKIS[4], C. BLACKSTONE[5], X.-J. LI[1]
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Abstract: Hereditary spastic paraplegia (HSP), a group of heterogeneous genetic disease, is characterized by progressive lower limb spasticity caused by the degeneration of cortical motor neuron axons. HSP Type 5 (SPG5), a form of HSP, is caused by mutations in the *CYP7B1* gene (cytochrome P-450 oxysterol 7-α-hydroxylase), which is involved in cholesterol metabolism. Generating patient-specific neurons from human iPSCs will offer unique tools to study axonal

defects, which gives future aspirations for the treatment. We hypothesize that patient-specific SPG5 neurons derived from human iPSCs mimic disease-specific axonal defects including reduced axonal outgrowth and impaired axonal transport. To test this hypothesis, we first generated SPG5 iPSC lines by transfecting fibroblasts cells with episomal plasmids containing pluripotent factors. PCR and qPCR analyses of the SPG5 iPSCs and fibroblast cells showed that the mRNA expression of stem cell markers (*NANOG, SOX2 and OCT4*) was highly enriched in iPSCs, but not in fibroblast cells. Moreover, these iPSCs uniformly expressed proteins of specific pluripotent stem cell markers (NANOG, SSEA4 and TRA-1-60), confirming the successful generation of iPSCs from SPG5 fibroblasts. Next, SPG5 and control iPSCs were induced to neural lineage and cortical projection neurons using a method established in our lab. Following differentiation, immunostaining analysis of neuronal proteins (TUBULIN and TAU) indicated successful generation of neurons from SPG5 and control iPSCs. Importantly, axonal outgrowth defects as indicated by reduced axonal length were observed in SPG5 neurons. In long-term cultures, SPG5 neurons exhibited increased formation of axonal swellings compared to that in control neurons, suggesting the accumulation of transported cargos along axons. Taken together, we successfully generated iPSCs from SPG5 patient fibroblasts and showed that these patient iPSC-derived neurons recapitulate the disease-specific axonal defects. This iPSC-based model of SPG5 provides a unique platform to further examine the role of lipid metabolism on axonal defects in SPG5 neurons and to explore the treatment for this disease.

Disclosures: G. Nandi: None. **Y. Mou:** None. **J.E. Nielsen:** None. **C. Criscuolo:** None. **M.J. Fraidakis:** None. **C. Blackstone:** None. **X. Li:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.21/B63

Topic: A.03. Stem Cells and Reprogramming

Title: Patients-specific stem cells for the investigation of psychiatric genetics

Authors: *M. JUNG[1,2], A. PULS[2], J. SCHILLER[2], A. KLEMENZ[3], C. HARTMANN[2], T. EHRHARDT[2], I. GIEGLING[2], D. RUJESCU[2]
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Abstract: Objectives: Schizophrenia is a psychiatric disease affecting about 1.1% of the world population. Treatment strategies need to be improved, but the molecular and cellular disease mechanisms are poorly understood. Copy number variations (CNVs) such as the heterozygous deletions have been associated with schizophrenia, which highly recommends detailed analysis

of the related cellular and molecular signaling pathways. Generation of induced pluripotent stem cells (iPS cells) provides an excellent approach to analyze disease mechanisms in patient-specific neural cells.
Material and Methods: Patient-specific iPS cells from schizophrenia patients carrying heterozygote deletions were established from B-lymphoblastoid cell lines (B-LCLs). Control iPS cell lines and schizophrenia-specific iPS cell lines were applied in a screening protocol for neural induction. Cell lines were differentiated into permanent neural stem cells (NSCs). NSCs were differentiated in 2D protocols and as free-floating neurospheres for the generation of 3D organoids. Transcript and protein analysis were applied for the characterization cells obtained from 2D and 3D protocols.
Results: Patient-specific iPS cells showed alkaline phosphatases activity and expressed pluripotency markers such as OCT4. Screening of iPS clones was necessary to identify clones with a high neural differentiation capacity. Patient-specific NSCs were successfully differentiated into progenitor cells expressing a variety of neural lineage markers including TUBB3 and GFAP. Protein expression analysis and patch-clamp recordings of mature neural cells showed the presence of different neuronal subtypes including inhibitory GABAergic neurons. NSCs were also successfully differentiated into 3D cerebral organoids. The expression pattern of cortical markers such as TBR1 revealed the induction of cortical layers mimicking the developing human cortex.
Conclusion: We could demonstrate that iPS cells carrying schizophrenia-associated DNA variations were successfully applied within neural differentiation protocols modeling aspects of the neural development of the human brain. These culture systems enable functional studies of healthy and diseased human cortical development enabling toxicological screenings and drug development in vitro.

Disclosures: **M. Jung:** None. **A. Puls:** None. **J. Schiller:** None. **A. Klemenz:** None. **C. Hartmann:** None. **T. Ehrhardt:** None. **I. Giegling:** None. **D. Rujescu:** None.

Poster

032. iPSCs: Disease Models

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Topic: A.03. Stem Cells and Reprogramming

Support: Knights Templar Eye Foundation Career Starter Award

Research to Prevent Blindness Career Development Award

Brightfocus Foundation

Foundation of Fighting Blindness Individual Investigator Award

Title: A retinal cell model of juvenile neuronal ceroid lipofuscinosis (JNCL , CLN3) derived from patient-hiPSCs

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Abstract: Juvenile neuronal ceroid lipofuscinosis (JNCL, Batten disease, CLN3) leads to progressive neurological dysfunction and retinal degeneration. Histopathologic studies have shown accumulation of autofluorescent lipopigment in retinal neurons and retinal pigment epithelium (RPE) and degeneration of multiple retinal cell layers in JNCL. However, the precise involvement of a specific retinal cell type in the disease and the underlying disease mechanism responsible for vision loss is not known. The purpose of this study was to determine the morphological and molecular consequences of JNCL in a patient-derived human induced pluripotent stem cell (hiPSC) retinal cell model of JNCL. hiPSCs were generated by reprogramming of fibroblasts from JNCL patients (1.02 kb deletion in *CLN3*) and unaffected family members. Pluripotency confirmed JNCL patient and control hiPSCs were differentiated to RPE and optic vesicles (OVs). OVs were harvested at day 20, 35, 55, and 90 coordinate with critical *in vivo* time points of retinal differentiation. Immunocytochemistry, qRT-PCR and Western blotting were utilized to determine 1) the spatiotemporal expression of CLN3, 2) autofluorescent lipopigment accumulation and 3) the differentiation and viability of neural retina (NR) cell types and RPE in patient vs. control cultures. CLN3 gene and protein expression peaked at the time point of OV formation (D20). Interestingly, CLN3 expression was altered in patient hiPSC OVs compared to control OVs at day 55 and day 90. Furthermore, an increased accumulation of autofluorescent material, corresponding to lipopigment excitation/emission spectrum, was seen in patient OVs and RPE. While, neural retinal progenitor cells gave rise to all NR cell types in control and patient OVs, gene and protein expression analysis suggested the specific loss of photoreceptor cells at day 90 in patient-derived OVs. In contrast expression of glial markers (S100, GFAP) was increased in patient-OVs compared to control OVs. Overall, this novel hiPSC retinal model of JNCL displays several important features consistent with the disease pathology including 1) autofluorescent material accumulation in NR and RPE, 2) decreased expression of neural retina markers in photoreceptors, bipolar cells and ganglion cells and 3) increased expression of glial markers and thus provides a unique platform to understand and manipulate the sequence of events that ultimately result in retinal degeneration in JNCL.

Disclosures: R. Singh: None. **S. Dalvi:** None. **L. Winschel:** None. **L. MacDonald:** None. **C. Galloway:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

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Topic: A.03. Stem Cells and Reprogramming

Support: NIH UL1 TR000433

NIH KL2 TR000434

NAMI Unger Family Fellowship

Heinz C Prechter Bipolar Research Program

NIH MH106434

Title: Spontaneous versus evoked calcium signaling in murine and patient-derived neurons

Authors: A. J. WILLIAMS[1], A. T. SMARSH[1], K. M. GLANOWSKA[2], V. A. CAZARES[3], L. OUILLETTE[4], C. DELONG[5], M. BAME[4], E. C. MARTINEZ[1], K.-C. LIM[4], R. PARENT[6], M. G. MCINNIS[1], G. G. MURPHY[7], *K. O'SHEA[8]
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Abstract: Bipolar disorder (BP) is a complex neuropsychiatric disorder which causes episodic alterations in mood, energy, and sleep. The molecular and cellular mechanisms of BP are not well understood. Patient-derived induced pluripotent stem cells (iPSC) offer the opportunity to examine the full complement of neural tissues, and the prospect of identifying underlying disease mechanisms. To study BP, we have derived and characterized iPSC from fibroblasts obtained from controls (C) and patients with BP, and have differentiated them into neurons and glia. Using fluorescent calcium indicators, we have measured differences in spontaneous and evoked calcium transients in neurons derived from BP patients and controls. While both BP and C neurons respond to depolarization, we find that BP neurons have greater calcium transients in response to certain types of stimulation than C neurons. We have also found that lithium pre-treatment reduces BP neuron calcium transients and wave amplitude to levels comparable to C neurons. It is thought that the majority of the observed calcium signal is the result of calcium influx though L-type voltage-gated calcium channels (LVGCCs). Importantly for our studies, single nucleotide polymorphisms in *CACNA1C*, the gene that encodes the LVGCC $Ca_V1.2$ have been repeatedly implicated as BP risk factors. Therefore, in a parallel set of experiments, we have begun to examine the role of $Ca_V1.2$ in calcium dynamics in vitro. To examine $Ca_V1.2$ localization and function in neurons, we used both spontaneous and evoked activity paradigms in $Ca_V1.2$ knockout mouse neurons. Our results suggest that $Ca_V1.2$ is differentially expressed within different neuronal compartments, and that its contribution to neuronal calcium signaling varies depending on the type of activity induction paradigm used. We are currently using our iPSC models to investigate the role of rs1006737, a single nucleotide polymorphism in the *CACNA1C* gene, in neuronal differentiation and function. We used the CRISPR/Cas9 genome editing system to edit BP cells with the rs1006737 risk genotype (AA) into the nonrisk (GG) genotype, and we are now assessing calcium signaling and differentiation potential in the

corrected cells. Our overarching goal is to use these mouse and human models to investigate calcium dynamics in BP in order to develop better therapies.

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Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.24/C1

Topic: A.03. Stem Cells and Reprogramming

Support: R01NS085272

R01NS42617

Title: Neurotrophic skin environment caused by direct reprograming of skin cells to neural cells may rescue against loss of neural fibers caused by diabetic peripheral neuropathy

Authors: A. CLARK, R. STEWART, N. HIGUITA-CASTRO, D. GALLEGO-PEREZ, S. ROY, C. SEN, *S. KHANNA
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Abstract: Diabetic complications represent a major threat, and peripheral neuropathy is one critical factor that complicates diabetic wound healing. Symptoms of diabetic peripheral neuropathy (DPN) include numbness or pain in the toes, feet, legs, hands and arms. In DPN, neurotrophin signaling mechanisms become dysfunctional with reported limitations in nerve growth factor (NGF) pathway. Our laboratory has recently discovered a non-viral technique to directly convert skin cells to electrophysiologically active neural cells in vivo. Such converted neural cells thrive on the skin and acquire electrophysiological functionality over four weeks. While some cells are converted because of our technique, what advances these neural cells from a fetal phenotype to functional adult cells is a neurotrophic environment in the skin contributed by non-converted skin cells caused by Ascl1, Brn2, and Myt1l (ABM) delivery. In this work, we ask can this neurotrophic environment be utilized rescue loss of neural cells during the course of DPN? Mouse embryonic fibroblasts (MEFs) were nanoelectroporated in vitro with ABM plasmids to induce direct conversion to neural cells. RT-PCR of ABM transfected MEFs showed greater expression of NGF as well as TUJ1 (immature neuronal marker) compared to MEFs transfected with a mock plasmid. In vivo, the hind limb skin of aged (7 month old) db/db mice was transfected with ABM plasmids. Diabetes was confirmed in these mice. Mice were

sacrificed 9 or 25 weeks after transfection. Skin biopsies were taken from the transfected sites and histologically analyzed for intraepidermal nerve fiber density and NGF levels. Intraepidermal never fiber density, determined by measuring the number of PGP9.5 positive nerve fibers per millimeter of epidermis, was significantly higher in the ABM transfected skin at week 9 after ABM delivery. NGF protein levels were also significantly increased in transfected skin compared to control at both 9 and 25 weeks post-transfection. These results provide first evidence that non-viral ABM delivery for direct conversion of dermal fibroblasts to neural cells results in a neurotrophic environment in the skin extracellular matrix milieu in a manner that may attenuate loss of neural cells caused by DPN.

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Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.25/C2

Topic: A.03. Stem Cells and Reprogramming

Support: NHMRC Australia 1025589

NHMRC Australia 1078943

Title: Using primary and stem cell derived sensory neurons in co-culture with airway epithelium to study mechanisms of sensory neuron plasticity in pulmonary disease

Authors: *J. A. KELLER[1], J. E. HUDSON[2], M. DOTTORI[3], G. A. MACKAY[4], A. E. MCGOVERN[5], S. B. MAZZONE[6]
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Abstract: The mucosa of the respiratory tree is densely innervated by sensory nerve fibres that monitor the local environment and contribute to pulmonary function and defense. Hypersensitivity of this sensory circuitry accompanies mucosal dysfunction in a variety of pulmonary diseases, and contributes significantly to patient morbidity. However, both the local mucosal mechanisms driving hypersensitivity and the accompanying phenotypic effects in sensory neurons are not well described, as it is difficult to study nerve-epithelium interactions *in vivo*. We set out to develop novel *in vitro* preparations consisting of primary vagal or stem cell

derived sensory neurons and human airway epithelial cells in order to assess mechanisms of sensory hypersensitivity and identify novel targets for alleviating the sensory-associated symptoms of lung disease. Murine primary vagal sensory neurons were enzymatically dissociated and cultured. Human embryonic stem cell (hESC) line H9 was differentiated into sensory neurons using small inhibitors (1-10μM SB-431542, 0.5-1μM LDN-193189, 1-10μM CHIR-99021, 1-10μM DAPT, and 1-10μM SU-5402) and matured using growth factors (10ng/ml BDNF, GDNF, NGF, and NT-3). Media conditions were optimised to allow epithelial cell line BCi-NS1.1 grown at air-liquid interface (ALI) to be co-cultured with sensory neurons. Immunohistochemistry and RT-PCR was used to characterize neurons and epithelial cells. hESC were successfully differentiated into neurons, positive for neurofilament 200/ b3-tubulin protein and key sensory marker genes (TAC1, SCN9A, P2RX3, TRPV1, ASIC2), and cultured for up to 32 days. Primary neurons co-cultured with differentiated epithelial cells at ALI possess significantly longer neurites than those grown alone (neurons only = 6.3±0.2 mm; co-culture = 10±1.0 mm; $P<0.05$) and have molecular expression profiles more similar to acutely isolated cells compared to neurons cultured for the same time alone. Altered growth and expression profiles of neurons in co-culture conditions is indicative of the existence of epithelial paracrine mediators in the co-culture system that evoke phenotypic changes in neurons. This project is ongoing and future experiments will utilise hESC-derived neurons and epithelial cells derived from patients with active respiratory diseases to better define mechanisms of sensory nerve plasticity in diseases.

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Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.26/C3

Topic: A.03. Stem Cells and Reprogramming

Title: Investigating the mechanisms underlying the beneficial effects of estrogens in schizophrenia

Authors: *P. M. DEANS[1], C. SHUM[1], A. B. PALMOS[1], F. ERLI[1], M. CONFORTI[1], R. R. DUARTE[1], P. RAVAL[1], J. A. CROWE[1], K. J. SELLERS[1], S. BHATTACHARYYA[2], T. R. POWELL[1], J. PRICE[1], D. P. SRIVASTAVA[1]
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Abstract: Estrogens have long been known to have an enhancing effect on a range of cognitive behaviours associated with neurodevelopmental disorders. This includes depressive and anxious

behaviours as well as learning and memory (including working memory). Data from our group and previous research have demonstrated that estrogen's ability to improve these cognitive behaviours is due in part to its influence on synaptic protein expression, thus resulting in long-term increases in synaptic connectivity.
In addition to these cognitive enhancing effects, estrogens have recently been reported to have beneficial effects in treatment of a range of psychiatric disorders. Importantly, recent clinical studies have demonstrated that adjunct treatment with 17β-estradiol (E2) or the selective estrogen receptor modulator (SERM) raloxifene, ameliorates positive and negative symptoms and improves working memory and attention deficits in male and female schizophrenic patients. However, the cellular and molecular mechanisms by which these beneficial effects occur are currently unknown.
Here, we have used a combination of primary neuronal cultures with human induced pluripotent stem cell (iPSC)-derived from healthy or schizophrenic patients to study the potential mechanism that may underlie estrogens beneficial effects in disease. Specifically, we have utilized a cellular model of neuropsychaitric disorders, in the form of manipulating the expression levels of the disrupted-in-schizophrenia 1 (Disc1) protein in mature primary rat cortical neurons. In parallel, we have generated cortical, forebrain-like neurons from iPSCs (iPSC-neurons). Using these cellular systems, we have first determine the validity of these cellular system to investigate estrogenic-based therapies. Subsequently, using a pharmacological approach, we have explored the ability of estrogens to rescue cellular and molecular deficits in primary neurons with altered DISC1 levels or in iPSC-neurons derived from schizophrenic patients. Collectively, we hope these data will help us understand how estrogens may confer their positive effects in psychiatric disorders.

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Poster

032. iPSCs: Disease Models

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Topic: A.03. Stem Cells and Reprogramming

Support: NIGMS grant T32GM007753

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NIMH grant R01MH101148

Title: Neurodevelopmental phenotypes in DISC1 disrupted hiPSC lines across multiple differentiation protocols

Authors: *V. LAGOMARSINO[1], P. SRIKANTH[2], C. R. MURATORE[3], W. M. TAYLOR[4], T. L. YOUNG-PEARSE[5]
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Abstract: Schizophrenia is a tragic psychiatric disorder hypothesized to arise from dysregulated neurodevelopment of proliferation, migration, neural patterning and synaptic regulation. Dirsupted- in- schizophrenia-1 (*DISC1)* has been implicated in psychiatric disease based on genetic studies, including its interruption by a balanced translocation that increases the risk of major mental illness. Stem cell technology has evolved to be a great tool to study neural development as new differentiation protocols are helping to elucidate the mechanisms by which certain mutations lead to mental illness. Here we analyzed three-dimensional cerebral organoid cultures, embryoid body derived neurons, as well as neurogenin-induced neurons (iNs) in a pair of isogenic wild-type/ *DISC1* disrupted hiPSC lines we generated using CRISPR-Cas9. We have examined the RNA profiles among our lines from each of these different protocols at developmentally similar time points. We then studied the morphological changes across the protocols and found *DISC1* mutated cerebral organoids display disorganized structural morphology and *DISC1* mutated iNs show altered patterns of neurite outgrowth. We further analyzed synaptic phenotypes of all lines by plating iNs on multi-electrode assays. By using these different protocols to generate neural cells, we can study the different processes of a *DISC1* disruption that relate to neurodevelopmental disorders.

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Poster

032. iPSCs: Disease Models

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Topic: A.03. Stem Cells and Reprogramming

Support: MINECO, Spain

Fundación Ramón Areces, Spain

Title: Effect of mutations in the GBA1 gene on the differentiation and maturation of iPSC-derived dopaminergic neurons

Authors: *C. VICARIO[1,2], E. RODRÍGUEZ-TRAVER[1,2], E. DÍAZ-GUERRA[1,2], L. SUAREZ[1,2], A. HERNANDEZ-VIVANCO[1], E. MORENO[1,2], P. FERNANDEZ[1,2], P. GARCIA-SANZ[1,2], F. ARENAS[2,3], P. VICARIO[1], M. ORIA[1,2], L. ORGAZ[1,2], C. CRESPO[4], C. RODRIGUEZ[5], M. ORERA[5], M. ARAUZO-BRAVO[6], J. KULISEVSKY[3,2], R. MORATALLA[1,2]

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Abstract: Mutations in the *glucocerebrosidase1* (*GBA1*) gene, which encodes a lysosomal enzyme are major risk factors for Parkinson´s disease (PD) and dementia with Lewy bodies. To investigate the impact of *GBA1* mutations on neuronal survival and maturation, we have generated induced pluripotent stem cell (iPSC)-derived dopaminergic neurons from PD patients carrying the N370S/wt and the L444P/wt mutations in the *GBA1* gene. The iPSCs maintained the original genotype, a normal karyotype, were free from Sendai viral genome, presented the typical iPSC morphology, expressed endogenous pluripotency markers (NANOG, OCT4, SOX2, TRA-1-60, and SSEA-4), and differentiated into endodermal, mesodermal and ectodermal cells. Dopaminergic neurons were generated from iPSCs by addition of growth factors and small molecules. The neurons expressed typical markers of mesencephalic dopaminergic neurons (including NURR1, FOXA2, LMX1A, LMX1B, and TH), acquired complex morphologies, released dopamine, expressed synaptic-associated proteins, fired action potentials and showed synaptic activity. These findings indicate that iPSC-derived dopaminergic neurons from GBA1-PD patients and control subjects reached a high degree of neuronal maturation. We are currently investigating alterations in the above-mentioned processes that could be attributable to the *GBA1* mutations.

Disclosures: C. Vicario: None. **E. Rodríguez-Traver:** None. **E. Díaz-Guerra:** None. **L. Suarez:** None. **A. Hernandez-VIvanco:** None. **E. Moreno:** None. **P. Fernandez:** None. **P. Garcia-Sanz:** None. **F. Arenas:** None. **P. Vicario:** None. **M. Oria:** None. **L. Orgaz:** None. **C. Crespo:** None. **C. Rodriguez:** None. **M. Orera:** None. **M. Arauzo-Bravo:** None. **J. Kulisevsky:** None. **R. Moratalla:** None.

Poster

032. iPSCs: Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 032.29/C6

Topic: A.03. Stem Cells and Reprogramming

Support: NIH grant 5U19MH104172

Title: Systematic analysis of schizophrenia-associated NRXN1 deletions using human pluripotent stem cell derived induced neurons

Authors: *C. PAK, S. GRIEDER, T. DANKO, A. HUANG, M. WERNIG, T. C. SUDHOF
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Abstract: Synaptic cell adhesion molecules mediate the physical and functional bridging of neuronal synaptic junctions. Neurexin-1 (NRXN1) is a presynaptic cell adhesion molecule that is essential for proper synapse formation and connectivity, and loss-of-function mutations in the human *NRXN1* strongly correlate with Autism Spectrum Disorders (ASDs) and schizophrenia (SZ). Recently, we have shown that in human induced neurons bearing conditional heterozygous mutations in *NRXN1* results in a specific deficit in the excitatory synaptic strength and neurotransmitter release probability, and in parallel, an up-regulation of calcium/calmodulin-dependent serine protein kinase (CASK) protein level. To investigate the functional relevance of these identified phenotypes in the context of neuropsychiatric disease, we have obtained, differentiated and analyzed a cohort of human induced pluripotent stem cells (iPSCs) from age and gender matched SZ patients carrying *NRXN1* deletions and healthy controls. Using the Neurogenin-2 induced neuronal protocol, which generates homogenous populations of cortical glutamatergic neurons, we are able compare functional differences in neuronal morphology, synaptic transmission, and gene expression with homogeneity and reproducibility.

Disclosures: C. Pak: None. **S. Grieder:** None. **T. Danko:** None. **A. Huang:** None. **M. Wernig:** None. **T.C. Sudhof:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 033.01/C7

Topic: A.05. Axon and Dendrite Development

Support: ALS Association

Travis Roy Foundation

Packard Center for ALS Research

Massachusetts Dept of Public Health

Title: Molecular controls over corticospinal motor neuron segmental targeting

Authors: *V. V. SAHNI[1], S. SHNIDER[1], D. JABAUDON[2], J. SONG[1], F. DING[1], J. D. MACKLIS[1]

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Abstract: The corticospinal system controls performance of skilled and complex movements. For precise motor control, distinct corticospinal motor neurons (CSMN) extend axons to, and innervate, distinct target spinal cord segments - from rostral targets in the brainstem and cervical cord (controlling face and forelimb movements) to caudal targets in the thoracic and lumbar cord (controlling hindlimb movements). The molecular basis for this segmentally specific connectivity is unknown.

We identified specific CSMN subpopulations that exhibit striking axon targeting specificity during development. We identified that CSMN in rostrolateral sensorimotor cortex extend axons exclusively to subcerebral targets in the brainstem and cervical spinal cord ($CSMN_{BC}$), and do not extend axons past these targets toward thoracic or lumbar cord. $CSMN_{BC}$ largely reside outside primary motor cortex (M1), comprise a significant subset of the total cortical projections to the cervical spinal cord, and exhibit distinct spinal connectivity from CSMN in M1 in the mature CNS. In complementary fashion, CSMN extending axons past the cervical cord toward thoracic and lumbar spinal segments ($CSMN_{TL}$) reside exclusively in medial sensorimotor cortex, residing entirely within M1.

We isolated $CSMN_{BC}$ and $CSMN_{TL}$ during development, and identified differentially expressed genes between them. Using this approach, we identified that:

1. CSMN subpopulations are molecularly distinct from the earliest stages of development.
2. Using transgenic Cre reporter mouse lines, we find that these molecular controls prospectively identify developing CSMN subpopulations that eventually extend axons to bulbar-cervical versus thoraco-lumbar segments.
3. Using intersectional mouse genetics, we additionally find that $CSMN_{TL}$ extend exuberant collaterals into cervical spinal segments. This indicates that mechanisms controlling CSMN axon targeting versus axonal collateralization to specific spinal segments are independent of one another.
4. We identify that a subset of these controls direct CSMN axons to appropriate spinal levels - bulbar-cervical extension by $CSMN_{BC}$ and thoraco-lumbar extension by $CSMN_{TL}$. These axon extension decisions occur prior to axonal collateralization, and therefore are independent of connectivity.

Together, these newly identified controls constitute new mechanisms directing CSMN axonal targeting. This work provides foundation for further investigation of mechanisms directing the development, regeneration, and evolution of precise corticospinal circuitry, and the roles of molecularly distinct CSMN subpopulations in voluntary motor control.

Disclosures: V.V. Sahni: None. **S. Shnider:** None. **D. Jabaudon:** None. **J. Song:** None. **F. Ding:** None. **J.D. Macklis:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 033.02/C8

Topic: A.05. Axon and Dendrite Development

Support: CTSI V097

Title: The role of Fezf2 in the postnatal cortical ventricular zone

Authors: *A. A. AKHTAR, G. KIM, N. KOBRITZ, H. PARK, M. CLARKE, R. LEVY, M. DANIELPOUR, J. J. BREUNIG
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Abstract: The transcription factor Fezf2 has been identified as a critical determinant of neuronal subtype specification, including layer 5 corticofugal projection neurons. This class of neurons includes corticospinal motor neurons that are lost in degenerative motor neuron disorders such as amyotrophic lateral sclerosis (ALS). Previous work has explored the ability of Fezf2 to reprogram cells to a corticofugal phenotype within a very spatial and temporal window of early development. Interestingly, Fezf2 is expressed by a large majority of dorsal ventricular zone (VZ) stem and progenitor cells, yet precious little has been done to elucidate the role of Fezf2 in this population. We have developed an electroporation-based method for stably expressing Fezf2 in neural stem cells lining the lateral ventricle. Increasing expression of Fezf2 in these cells reduces astrogliogenesis and olfactory bulb (OB) neurogenesis. To avoid these acute OB neurogenesis alterations, we developed an inducible and reversible, 3rd generation, doxycycline(Dox)-regulated genetic system for expressing Fezf2. When Fezf2 expression is induced postnatally in the olfactory bulb, we see changes in nuclear size, increased ER81 expression, and evidence of ectopic axonal growth from the olfactory bulb. Using this new technology, we are exploring the ability of Fezf2 to reprogram heterogeneous populations of stem, progenitor and terminally differentiated cells to corticofugal subtypes in postnatal and adult mice.

Disclosures: A.A. Akhtar: None. **G. Kim:** None. **N. Kobritz:** None. **H. Park:** None. **M. Clarke:** None. **R. Levy:** None. **M. Danielpour:** None. **J.J. Breunig:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

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Program#/Poster#: 033.03/C9

Topic: A.05. Axon and Dendrite Development

Support: ALS Association

Travis Roy Foundation

Massachusetts Department of Public Health – SCI Cure

Title: Molecular controls over corticospinal motor neuron axonal branching at specific spinal segments

Authors: *Y. ITOH, V. SAHNI, S. J. SHNIDER, F. DING, J. D. MACKLIS
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Abstract: Corticospinal motor neurons (CSMN, and related cortico-brainstem neurons; together "CSMN") are located in layer V of the neocortex, and make synaptic connections with circuitry in the spinal cord and brainstem. CSMN axons form the corticospinal tract (CST), the major motor output pathway from the cerebral cortex essential for voluntary motor control. CSMN are also clinically important. CSMN degeneration in amyotrophic lateral sclerosis (ALS), along with degeneration of spinal motor neurons, causes spasticity and paralysis. In humans, damage to the CST in spinal cord injury is the principal cause of loss of voluntary motor control. Previous studies in our lab have identified combinatorial molecular controls over the specification and differentiation of CSMN.

CSMN themselves exhibit striking anatomical and functional diversity: Some CSMN extend axons to innervate cervical spinal cord targets and control forelimb movement, while others extend far more caudally to innervate lumbar segments and control hindlimb movement. We genetically labeled a CSMN subpopulation extending their axons to the thoracic and lumbar segments ($CSMN_{TL}$) and identified that their mature axons develop gray matter innervation at all spinal segmental levels. Further, we identified a secreted proteoglycan expressed specifically by bulbar-cervical-projecting CSMN ($CSMN_{BC}$) that non-cell-autonomously limits $CSMN_{TL}$ axonal collateral branching in the cervical spinal cord. These results identify extensive innervation by $CSMN_{TL}$ in the spinal cord, as well as a novel mode of control over circuit connectivity. This non-cell-autonomous regulation of $CSMN_{TL}$ axonal branching by $CSMN_{BC}$ identifies a new class of molecular mechanism over development of segmentally and functionally specific corticospinal and potentially other CNS circuitry.

Disclosures: **Y. Itoh:** None. **V. Sahni:** None. **S.J. Shnider:** None. **F. DIng:** None. **J.D. Macklis:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

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Program#/Poster#: 033.04/C10

Topic: A.05. Axon and Dendrite Development

Support: NJ Commission on Spinal Cord Research grant

Title: Analysis of developing axonal projections to and from the mammalian spinal cord using the iDisco tissue clearing protocol

Authors: *E. MARTINEZ[1], G. RALDA[1], Z. WU[2], T. S. TRAN[1]
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Abstract: The proper pathfinding of axons towards their final target is a complex process that involves the coordinated activity of intrinsic and extrinsic cues. The developing spinal commissural neurons are an excellent model system for the study of axon guidance due to their stereotypic projections. During mammalian spinal cord development, these neurons extend their axons along the dorsal-ventral axis towards the ventral floor plate, cross the midline, and turn in the anterior-posterior axis towards their rostral targets. Previous studies have uncovered several molecular mechanisms to explain various aspects of the axon guidance events of spinal commissural axons, however, little is known about their precise path towards their final targets. To explore the final targets of these axons, we have employed a strategy that makes use of transgenic mouse reporters that specifically tag subpopulations of dorsal spinal commissural neurons and their axons, in combination with the iDisco tissue clearing protocol. Using this protocol, whole embryos can be processed for immunohistochemistry and imaged using confocal microscopy providing the advantage of observing developing axon tracts in the preserved environment. Furthermore, growing axons depend on the availability and the proper trafficking of specific receptors on their axonal/growth cone surface to respond to the variety of external cues presented along their trajectories. Therefore, we have begun to characterize the role of the small GTPase family of Rabs during spinal cord development. In particular, Rab11b is expressed in the nervous system and functions as part of the recycling endosome to regulate vesicular trafficking to and from the plasma membrane. Perturbation of Rab11 *in vitro* has been shown to lead to alterations in dendritic or axonal growth, however, little is known about the role of *Rab11 in vivo.* Here we examine *Rab11b* knockout mice, focusing on axonal guidance events within the developing spinal cord. Taken together our approaches and results will provide a better understanding of the path that spinal commissural axons take en route to their final targets, and

novel insights of the molecular mechanisms that are essential for axon guidance events *in vivo*. This study is supported by the NJ Commission on Spinal Cord Research grant to TST.

Disclosures: E. Martinez: None. **G. Ralda:** None. **Z. Wu:** None. **T.S. Tran:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

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Topic: A.05. Axon and Dendrite Development

Support: SIB Training Grant T32GM07517

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March of Dimes

Klingenstein Foundation

University of Pennsylvania

Title: Roof plate-derived dorsal midline radial glial cells promote spinal cord dorsal column longitudinal axon growth during development

Authors: *K. KRIDSADA[1], J. NIU[4], Z. WANG[2], P. HALDIPUR[5], L. DING[1], J. J. LI[3], E. HERRERA[6], K. J. MILLEN[5], G. M. THOMAS[4], W. LUO[1]
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Abstract: The ability to regenerate the central nervous system is limited to only a subset of vertebrates, such as amphibians and fish. In these robustly regenerating species, radial glial cells (RGCs) in the spinal cord are hypothesized to construct stereotyped channels that precede neurite outgrowth, providing a growth permissive environment during both regeneration and development. In rodent spinal cords, RGCs similarly grow a fibrous network of highly conserved compartments during embryonic stages when axon tracts begin to form. However, whether mammalian RGCs play similar roles in developmental longitudinal axon growth, and whether this mechanism can be harnessed to promote spinal cord regeneration, remains largely unknown.

By studying mechanisms underlying CNS development, we hope to provide novel insight into regeneration. Our lab has identified a population of roof plate-derived radial glial cells that migrate into the dorsal midline of the mouse spinal cord during embryonic growth of dorsal column (DC) axons from E14.5. These dorsal midline radial glial cells (DMRGs) lie in close apposition to the longitudinally growing DC fibers, which are the ascending axons of mechanoreceptors in the dorsal root ganglia. Their proximity to the fibers suggests a potential cell-axon interaction in promoting growth. Through RNA sequencing, we show that the DMRGs express growth promoting factors during development that are sufficient to induce axon outgrowth. By examining a mouse line carrying a mutation in *Lmx1a*, a gene required for roof plate development, we show that ascending DC fibers are shortened in *Lmx1a*-null mice, and fail to reach their targets in the medulla. These deficits, in conjunction with their scaffold-like morphology, suggest that DMRGs provide mechanical and chemical support to promote longitudinal growth and pathfinding of developing DC fibers. Our findings reveal a novel developmental mechanism in the mammalian system for long distance growth and guidance throughout the spinal cord.

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Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

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Program#/Poster#: 033.06/C12

Topic: A.05. Axon and Dendrite Development

Support: the National Natural Science Foundation of China (numbers 81330026, 31271259, 30990261, 30871425)

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Title: Ryk regulates Wnt5a repulsion of mouse corticospinal tract through modulating planar cell polarity signaling

Authors: *Y. LIU, X. DUAN, Y. GAO, *Y. LIU
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Abstract: It was previously reported a role for Ryk in mediating Wnt5a repulsion of the corticospinal tract (CST) in mice. Recent evidence has shown that Ryk regulates planar cell polarity (PCP) signaling through interacting with Vangl2. Here, *in vivo*, *in vitro* and biochemical analyses were applied to investigate the molecular cross-talk between the Ryk and PCP signaling pathways, revealing that PCP pathway components play important roles in CST anterior-posterior guidance. Ryk-Vangl2 interactions are crucial for PCP signaling to mediate Wnt5a repulsion of CST axons. Cytoplasmic distribution of Ryk is increased under high concentrations of Wnt5a and facilitates the cytoplasmic distribution of Vangl2, leading to inhibition of Frizzled3 translocation to cytoplasm. Alternatively, Ryk stabilizes Vangl2 in the plasma membrane under low Wnt5a concentrations, which promotes cytoplasmic translocation of Frizzled3. We propose that Ryk regulates PCP signaling through asymmetric modulation of Vangl2 distribution in the cytoplasm and plasma membrane, which leads to repulsion of CST axons in response to the Wnt gradient.

Disclosures: **Y. Liu:** None. **X. Duan:** None. **Y. Gao:** None. **Y. Liu:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

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Topic: A.05. Axon and Dendrite Development

Support: Fondation pour la Recherche Médicale (FRM 2014 DEQ20140329557)

Agence Nationale de la Recherche (ANR 16 CE 16 0019 01 NEUROTUNN)

E-Rare/ERANET (project SIRD)

Title: Non canonical Wnt signaling pathway modulates tunneling nanotubes formation in neurons and neuron-like cells

Authors: *J. Y. VARGAS[1], G. CÓRDOVA[2], Y.-J. WU[1], C. TROLLET[2], C. ZURZOLO[1]
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Abstract: Tunneling nanotubes (TNTs) are F-actin-based transient tubular connections that allow direct communication between distant cells. Recent studies have implicated TNTs in key processes, such as development, immunity and tissue regeneration, but also in the transmission of several pathogens. TNTs can arise from the extension of filopodia-like protrusions towards neighboring cells, a process in which actin polymerization plays an important role. In this work, we have studied whether Wnt pathway, an intracellular cascade that is involved in actin cytoskeleton remodeling, could have a role on TNT formation and TNT-mediated vesicle

transfer. To this aim, we used activators of both canonical and non-canonical Wnt pathways in neuronal CAD cells and in primary neurons. Lithium, a pharmacological inhibitor of GSK3β, was used to activate the canonical Wnt pathway and the recombinant Wnt7a protein was used to activate the non-canonical Wnt pathway in CAD cells. We found that Wnt7a, but not lithium, increases TNT formation and vesicle transfer between CAD cells. Moreover, the effects of Wnt7a were abolished by inhibitors of JNK and CaMKII, suggesting that both non-canonical Wnt/JNK and Wnt/Ca^{+2} pathways are mediating the effects of Wnt7a. The effect of Wnt7a and Wnt5a recombinant proteins in TNT formation and vesicle transfer were also tested in hippocampal neurons. We found that the activation of the non-canonical Wnt pathway also modulates the formation of TNT-like connections between neurons. Overall, our data suggest that non-canonical Wnt pathway can modulate TNT formation in neurons and neuron-like cells. The results presented here open a path for the development of new therapeutic strategies to impair the interneuronal propagation of pathogens that spread throughout the brain via TNTs.

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Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

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Program#/Poster#: 033.08/C14

Topic: A.05. Axon and Dendrite Development

Support: MWU Intramural multidisciplinary research award

Title: Submicron topographic cues on quasi-2D and 3D substrates to enhance directional axon outgrowth

Authors: *M. FORNARO[1], R. GARCIA[2], C. SIGERSON[3], S. VEEN[2], C. LIU[5], P. NEALEY[5], H. SHARTHIYA[4], K. KRISTJANSDOTTIR[2], J. GASIOROWSKI[2]
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Abstract: Peripheral nerve injury is a debilitating disease characterized by loss of sensation and/or motor function at the affected site. Although fibers in the peripheral nervous system spontaneously regenerates after injury, in many cases, full functional restoration is not achieved. One likely explanation is that regenerating fibers do not reach the peripheral target because of their propensity to grow in undesired directions in the absence of proper biochemical and biophysical cues. Therefore, the aim of this study is to optimize directional axon outgrowth using surfaces with nano- to micro-scale anisotropic topographic patterns as a biophysical guide.

Previous work in our lab has shown that mouse dorsal root ganglia (DRGs) cultured ex vivo on surfaces with repeating groove widths of 700 nm or 2000 nm had significantly longer and more controlled axon outgrowth than flat surfaces. Our hypothesis is that not only directionality bur also speed of axon growth parallel to the grooves will be enhanced.
For this study we harvested and cleaned cervical and thoracic DRGs from mice and cultured them on chemically identical 2-D surfaces, with a groove width of 700nm as well as a flat control. Axon growth was observed every 6 minutes for 24 hours in time-lapse 72-96 hours after initial plating in phase contrast microscopy. Angles of growth relative to the grooves and axon growth speeds were analyzed using ImageJ. Additionally, DRGs were similarly cultured in 5 mm diameter 3-D half-tube structures with 700 nm grooves, 2000 nm grooves, and flat controls on the inner wall. DRGs were immune-labelled and imaged 6 days after initial plating using fluorescence microscopy. The longest axons were measured from the center of each DRG body in ImageJ. Various images were deconvolved and modeled in 3D with ImageJ to visualize the 3D growth of axons in the half-tubes.
In summary, our analysis indicates that DRGs grown on topographic surfaces exhibit significantly more directional axon growth parallel to the grooves compared to the flat control, as well as a marginally faster axon growth speed. In addition, also using our 3-D model, the axonal growth is more controlled and oriented parallel to the grooves. Moreover, fibers grown on half-tubes with inner-wall topography exhibited longer axon outgrowth than control.
Our results may be used to better understand the various mechanisms of peripheral nerve regeneration and applied towards the fabrication of implantable, fully enclosed tubes with specialized topography to ultimately restore nerve function.

Disclosures: **M. Fornaro:** None. **R. Garcia:** None. **C. Sigerson:** None. **S. Veen:** None. **C. Liu:** None. **P. Nealey:** None. **H. Sharthiya:** None. **K. Kristjansdottir:** None. **J. Gasiorowski:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 033.09/C15

Topic: A.05. Axon and Dendrite Development

Support: Smoking Research Foundation

Title: Dual effect of nicotine on neurite outgrowth of rat superior cervical ganglia cells and PC12 cells

Authors: *H. KAWASAKI[1], S. TAKATORI[2], Y. KONDO[2], H. SAGARA[2], H. HINO[3], F. TAKAYAMA[3], Y. KITAMURA[4], T. SENDO[4]
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of Clin. Pharmaceut. Sci., Grad. Sch. of Medicine, Dent. and Pharmaceut. Sciences, Okayama Univ., Okayama, Japan; [4]Okayama Univ. Hosp., Okayama, Japan

Abstract: ***Background****:* We have reported that nicotine reinnervates only perivascular sympathetic adrenergic nerves lesioned by topically applied phenol in the rat mesenteric artery *in vivo*, and markedly increased levels of nerve growth factor (NGF) contents and the expression of NGF receptor TrkA in superior cervical ganglia (SCG), which were inhibited by the pretreatment of nicotinic acetylcholine receptor (nAChR) antagonist hexamethonium (Takatori S *et al*., Eur J Pharmacol, 748: 1-9, 2015.). Furthermore, we demonstrated that nicotine increases neurite outgrowth of SCG via activation of α7 nAChR *in vitro*. To clarify possible mechanisms, the present study further investigated the effect of nicotine on neurite outgrowth of primary cultured-SCG cells and PC12 cells *in vitro*. ***Methods****:* SCG cells isolated from Wistar neonate rats and PC12 cells were primarily cultured for 5 days. Numbers and length of neurite outgrowth from cell body were measured in the presence of nicotine (0.01-100 mM). Hexamethonium (100 μM) or α-bungarotoxin (100 nM) was co-incubated with each concentration of nicotine (1-100 mM) for 5 days. ***Results****:* Nicotine at a concentration of 0.01-0.1 mM increased numbers of neurite outgrowth from tyrosine hydroxylase-immunopositive SCG cells, while nicotine-induced neurite increase was gradually reduced by high concentration of 0.3-10 mM and the numbers at 1-10 mM nicotine decreased than that of the control. The α7 nAChR antagonist α-bungarotoxin (100 nM) inhibited the nicotine-induced increase in neurite numbers, but the antagonist did not inhibit decrease in neurite outgrowth numbers, which were inhibited by hexamethonium. In PC12 cells, nicotine at low concentrations (0.01-1 mM) caused a concentration-dependent increase in numbers and length of neurite outgrowth, which were inhibited by hexamethonium. However, higher concentrations (10-100 mM) of nicotine decreased numbers and length of neurite outgrowth compared to control in a concentration-dependent manner. ***Conclusion****:* These results suggest that nicotine has a neurotropic action, but it has dual action that is facilitatory and inhibitory mechanisms in neurite outgrowth (This study was supported by Smoking Research Foundation).

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Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

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Topic: A.05. Axon and Dendrite Development

Support: Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health P20GM0103423

Title: Characterization of semaphorins in developmental and adult plasticity

Authors: *H. W. HORCH[1], H. P. FISHER[1], D. ZAMBRANO[1], S. SPICER[1], L. SAIDENBERG[1], M. CHONG[1], L. LEDWIDGE[1], S. JIMENEZ[1], S. KNIGHT[1], J. MOYNIHAN[1], M. G. PASCUAL[2], A. E. CHRISTIE[2]
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Abstract: The axons and dendrites of the nervous system require specific instructions from several families of guidance molecules during development. In the adult, these cues are sometimes present and are likely used to balance maintenance and plasticity. In order to understand the molecular and mechanistic differences between developmental and adult plasticity, we have turned to the cricket, which displays an unusually robust injury-induced anatomical plasticity in its auditory system. However, little is known about the molecular control of either nervous system development or adult compensatory plasticity in this organism. We have mined transcriptomes from the cricket, *Gryllus bimaculatus*, for orthologues of the semaphorins, a well-conserved family of guidance molecules that play important roles in developing and adult nervous systems. We have found well-conserved isoforms of sema1, 2, and 5. Sequence analysis and *in situ* hybridization have allowed us to characterize expression patterns of several semas in developing embryos and in adult nervous tissue, including two different sema1a isoforms, which we identify here. The different roles these semas play in development of the central and peripheral nervous system were explored using dsRNA and anti-HRP immunohistochemistry. In the adult prothoracic ganglia, differential expression of sema1a and 2a correlates with unilateral removal of the ear. We asked whether the semaphorins might play an instructive role in the injury-induced auditory plasticity by knocking down semas *via* dsRNA injections, backfilling auditory neurons, and examining their morphology. Our findings indicate that changes in the expression levels of semaphorins are likely important in both development and adult plasticity.

Disclosures: H.W. Horch: None. **H.P. Fisher:** None. **D. Zambrano:** None. **S. Spicer:** None. **L. Saidenberg:** None. **M. Chong:** None. **L. Ledwidge:** None. **S. Jimenez:** None. **S. Knight:** None. **J. Moynihan:** None. **M.G. Pascual:** None. **A.E. Christie:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 033.11/C17

Topic: A.05. Axon and Dendrite Development

Support: NIH ROI EY025205

Title: Slit/Robo signals control two guidance steps of oculomotor (III) and trochlear (IV) nerve growth to the eye

Authors: *C. M. GARCIA-PENA, G. E. ROBINSON, L. NUNES, B. BJORKE, M. KIM, G. S. MASTICK
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Abstract: The alignment and the movement of the eye is controlled by precise innervation of eye muscles by three cranial nerves: oculomotor nerve, trochlear nerve and abducens nerve; alteration of the connectivity of these nerves can lead to strabismus and eye movement disorders. However, the molecular and cellular mechanisms that guide cranial nerve axons to the eye remains poorly understood. Our current project considers if Slit/Robo signaling controls the navigation of the oculomotor nerves. To test the guidance function of Robos and Slits, we mapped the expression of the proteins, and analyzed Robo1-/- 2-/- and Slit 1-/- 2-/- mutant mice from embryonic stage (E)9.5 to E14.5. We found that Slit1 and 2 are expressed in the ventral areas of the neural tube, and in the eye and surrounding tissue. On the other hand, Robo1 and 2 are expressed by oculomotor axons. In wild type embryos, the oculomotor nerve develops in two main stages of navigation. In the first step, from E9.5 to E10.5, axons projected out of the neural tube, forming a pathway from the midbrain to the eye, in a space between the face and the forebrain, where the axons formed a plexus in contact with a mass of eye muscle precursors. The second step, from E12.5 to 14.5, the oculomotor plexus formed branches that bifurcated to the dorsal and ventral part of the eye. In Slit/Robo mutants, we found alterations in both steps. In the nerve pathway, axons defasciculated in early stages of projection to the eye, but in later stages, the axons recovered to align to form a compact single nerve. For the second step, in Slit/Robo mutants, some axons passed the ventral plexus area, while others axons looped or spread out of the plexus area, far away from the eye. We found similar requirements for Slit/Robo signaling in trochlear nerve formation. In wild type embryos, trochlear axons projected out from the hindbrain at 10.5 and contacted muscle precursors near the dorsal part of the eye at E12.5. During this navigation, trochlear axons spread broadly and in parallel, but later fasciculated into a compact nerve. Analyzing Slit/Robo mutants, we found that at E11.5 the trochlear failed to fasciculate and they did not reach the dorsal area of the eye. Instead, axons projected toward the dorsal boundaries of the face and telencephalon. Our results suggest two different steps that Slit/Robo signals control for both cranial nerves: one, the axon/axon contact in the nerve pathway to the eye, and second, the plexus area of contact with the muscle precursor. Further investigation is required to uncover how Slit/Robo signals promote fasciculation of the tracts, and, on the other hand, how these signals guide the close association of the terminal branches with the muscles.

Disclosures: C.M. Garcia-Pena: None. **G.E. Robinson:** None. **L. Nunes:** None. **B. Bjorke:** None. **M. Kim:** None. **G.S. Mastick:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

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Program#/Poster#: 033.12/C18

Topic: A.05. Axon and Dendrite Development

Support: CIHR GRANT #366649

Title: Is netrin-1 a long-range chemoattractant?

Authors: C. P. CHEUNG, K. LAI WING SUN, S. HARRIS, *T. E. KENNEDY
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Abstract: Gradients of secreted long-range attractant and repellent proteins have been proposed to guide growing axons during neural development. In the embryonic spinal cord, commissural axons pioneer a circumferential trajectory to the floor plate at the ventral midline in response to multiple extracellular cues. These include dorsally secreted repellent BMPs and ventrally derived attractants netrin-1 and sonic hedgehog. Netrin-1 is expressed by cells in the ventricular zone and floor plate, and is essential for commissural axon guidance *in vivo*. Recent findings have demonstrated that netrin-1 made by ventricular zone progenitor cells is critical for commissural axon extension to the midline. These studies also purport to rule out a role for netrin-1 secreted by floor plate cells as a long-range cue, instead providing evidence for a short-range distribution of ventricular zone progenitor cell derived netrin-1 that promotes axon extension along a permissive corridor. Here, we examined the localization of netrin-1 protein in the embryonic spinal cord. We detect a graded distribution of floor plate derived netrin-1 protein that is distributed many cell diameters, hundreds of microns, away from netrin-1 expressing cells, the defining characteristic of a long-range cue. Further, we show that manipulating the distribution of netrin-1 within the embryonic spinal cord severely disrupts commissural axon guidance. This demonstrates that the precise distribution of netrin-1 protein is critical to its guidance function. Our findings support the operation of netrin-1 as long-range chemoattractant that, in collaboration with floor plate derived sonic hedgehog, directs axons to the ventral midline of the embryonic spinal cord.

Disclosures: C.P. Cheung: None. **K. Lai Wing Sun:** None. **S. Harris:** None. **T.E. Kennedy:** None.

Poster

033. Axon Growth and Guidance: Extrinsic Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 033.13/C19

Topic: A.05. Axon and Dendrite Development

Title: The role of microRNAs in the neurotoxic effects of early-life anesthetic exposure

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Abstract: Introduction:
Converging evidence, including work from our lab, has shown that neonatal exposure to volatile anesthetics impairs social and cognition behaviors during adulthood. However, a lack of mechanistic understanding is hindering the progress toward treatment. Our lab is investigating brain microRNAs (miRNAs) as a putative mechanism underlying the neurotoxic effects of neonatal volatile anesthetic (sevoflurane) exposure. Brain miRNA are critically involved in the fine-tuning of gene expression in a spatiotemporal manner. We hypothesize that perturbation by sevoflurane (sevo) during early development results in aberrant expression of selective brain miRNAs, thus leading to the observed changes in behavior.
Methods:
Postnatal day 7 (P7) male mice were exposed to 2-2.3% sevo for 2 hours. Brain tissue was harvested either immediately after (P7-P7 group) or when the mice reached adult age (P7-adult group). miRNA profiling and Real-Time PCR were used to examine miRNA expression. Bioinformatics was used for the analysis of Kegg Pathway and Biological Process (David Database 6.7). For axon growth analysis, green Fluorescent Protein plasmid was co-transfected in primary cortical neurons. Map2 antibody (Abcam) was used to characterize dendritic branching.
Results:
miRNA profiling of the P7-P7 group was performed based on the known 599 brain miRNAs. It was the difference between brain regions, comparing the whole brain and the hippocampus, independent of sevo treatment, which resulted in the least correlating/highest contrast of miRNA expression patterns. As a result of sevo treatment, we identified 6 distinctive miRNAs that were differentially expressed in each of the hippocampus and the whole brain P7-P7 groups. Interestingly, the differential expression of these selective miRNAs continued into the P7-adult group, which also showed significantly increased expression compared to the P7-P7 group. Bioinformatic analysis showed that these miRNAs targeted genes are critically involved in early brain development, such as axon guidance. Morphologically, application of miRNA 145 inhibitor (one of the differentially expressed miRNAs) in cultured neurons resulted in reduction

of axonal growth and dendritic branching.
Conclusions:
Our data elucidated that neonatal sevo exposure alters miRNA expression throughout development. Regulation of sevo-associated miRNAs could be crucial for the morphological development of the brain. The results of this study are a stepping stone toward future therapeutic interventions in pediatric anesthesiology.

Disclosures: S.S. Phatarpekar: None. **J. Liu:** None. **J. Cottrell:** None. **I.S. Kass:** None. **D. Lin:** None.

Poster

034. Autism: Behavioral Analysis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 034.01/C20

Topic: A.07. Developmental Disorders

Support: Hartwell Foundation Individual Biomedical Award

Brain and Behavior Foundation NARSAD Young Investigator Award

NICHD U54 HD090256

NICHD P30 HD003352

Title: Motor symptoms in autism are associated with abnormal tissue microstructure in the brainstem

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Abstract: Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder affecting 1 out of 68 people in the US. Alongside the core symptoms, >50% of children with ASD have comorbid motor impairments. If spotted early during development, motor impairments are predictive of an autism diagnosis and can facilitate early interventions. However, the neurobiological causes of motor challenges in ASD are poorly understood. We have previously reported that motor impairments in ASD are associated with microstructural atypicalities in the brainstem. However, until recently, we have not had the technology to examine specific structures within the brainstem. Here, we use brainstem-optimized neuroimaging methods to assess which brainstem substructures are associated with motor challenges in ASD.
Objective: To examine microstructure in select white matter tracts of the brainstem in children

with and without ASD and how it relates to motor symptoms.
Methods: The study involved more than 40 children with and without ASD (ages 6-10 years). Quantitative T1-weighted scans were combined with brainstem-optimized DWI images to achieve precise segmentation of the brainstem substructures. Tissue microstructure was assessed by calculating fractional anisotropy (FA), axial, mean, and radial diffusivity in select ROIs of the brainstem (using MRTrix software for segmentation). A hand dynamometer measured grip strength. Balance and motor profiles were obtained *via* the BOT-2.
Results: We report distinct relations between motor profiles and brainstem tissue microstructure in children with ASD compared to children without ASD. In children without ASD, grip strength was positively associated with FA of both the ascending and descending white matter tracts in the brainstem (medial lemniscus and pyramidal tract, respectively). Children with ASD showed a similar *positive* association between the motor profile and ascending brainstem pathways. However, the descending pyramidal tract FA was *negatively* correlated with grip strength in ASD.
Conclusions: These data provide evidence for brainstem involvement in motor impairments in ASD. The present results further suggest that the descending brainstem pathways may be a critical factor in the weak grip strength commonly reported in ASD. Further analyses will examine broader motor profiles in ASD as a function of the microstructure of additional brainstem nuclei.

Disclosures: O. Dadalko: None. **K. McLaughlin:** None. **B. Travers:** None.

Poster

034. Autism: Behavioral Analysis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 034.02/C21

Topic: A.07. Developmental Disorders

Support: Research Seed Grant, Southern Illinois University School of Medicine

Title: Enhanced audiovisual integration and perception of social robots for children with autism spectrum disorders (ASDs)

Authors: *D. K. SARKO[1], A. PERRY[1], K. D. SUDHEIMER[2], B. CAIN[1], K. WILLS[1], E. WOLFE[3], J. WEINBERG[3], F. SARTORATO[4]
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Abstract: Ineffective sensory integration - particularly for complex stimuli, such as speech - is thought to be a contributing factor in the communication and social interaction deficits characteristic of autism spectrum disorders (ASDs). Social communication inherently relies on effective integration of audiovisual cues to generate accurate perception and guide appropriate behavioral responses. Recent studies have shown that social robots are useful tools for social skill improvement and communication therapy for children with ASD. In the current study, we hypothesized that a humanoid robot with limited vocal, facial, and body expressions may be effective because it offers a more simplified version of a human interaction that is easier for children with ASD to perceive. To test this, we examined how effectively human vs. robotic audiovisual stimuli are perceived by typically developing (TD) children compared to children with ASD. We predicted that children with ASD would exhibit larger temporal binding windows (TBWs, a measure of sensory integration acuity) compared to TD children in response to human stimuli, since previous studies have shown that individuals with ASD have difficulty integrating complex audiovisual stimuli such as speech. We further predicted that children with ASD would exhibit narrower TBWs (enhanced audiovisual integration) for social, humanoid robot stimuli compared to human stimuli, since the social cues and body language of human interactions can distress, confuse, and overwhelm individuals with ASD. Our preliminary data support these hypotheses. Children with ASD exhibited enhanced audiovisual integration (narrower TBWs) for social robot compared to human stimuli. This may be due to the simplified versions of social communication (e.g., speech and body language) conveyed by humanoid robots in a more "perceptually palatable" form for children with ASD. Interestingly, the TBW size for robotic stimuli in children with ASD was similar to that of TD children for both human and robotic stimuli. This suggests that children with ASD may process sensory information from robots as effectively as TD children process human or robotic stimuli. By improving our understanding of how children with ASD perceive social stimuli and integrate sensory cues, such studies can be used to extend the therapeutic benefits of social robots and potentially generalize these benefits to improve human social communication.

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Poster

034. Autism: Behavioral Analysis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 034.03/C22

Topic: A.07. Developmental Disorders

Support: Departmental funds

Title: Quantifying and aligning activity profiles between therapists and children with autism spectrum disorder during sensory integration therapy

Authors: *C. M. HOLLAND, E. I. BLANCHE, B. L. THOMPSON
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Abstract: Sensory integration therapy (SIT) is widely employed by occupational therapists (OT) with clients with autism spectrum disorder (ASD) and is frequently requested by parents of children with ASD. SIT builds on a neurodevelopmental understanding of how higher-order circuits are formed, and thereby emphasizes remediation of sensory foundations to improve higher-order functions. Recent research provides compelling support for SIT as an effective intervention for improving both sensory-related and functional difficulties in children with ASD, though there continue to be discrepancies in what constitutes SIT and optimal dosage of SIT. The goal of this set of studies was to provide a comprehensive quantification of behaviors elicited by both the therapists delivering the intervention as well as the child receiving the intervention. Intervention was provided at two local occupational therapy clinics in the Los Angeles area by an OT with advanced training in SIT. Videotaped SIT sessions were analyzed using continuous sampling behavior coding with the Observer XT (Noldus Information Technologies, The Netherlands). Individualized and comprehensive coding schemas for the child and the therapist were created. For the child, a coding schema with 190 behaviors was created, and included behaviors relevant to sensory processing as well as behaviors relevant to ASD core symptomology. For the therapist, a schema of 140 behaviors including type, quantity, and quality of sensory interactions provided as well as social interactions with the child was created. Our data revealed a decrease in behaviors related to core ASD symptoms in the child during the last intervention session as compared to the first session. In comparison, our data reveals that therapists in clinical settings provide children with a variety of sensory stimuli during a session and are utilizing a rich verbal repertoire of behaviors throughout SIT. Investigations to establish temporal relationships of therapist initiated actions, such as providing sensory stimuli, on the behavioral outcomes of the children during SIT activities are currently being conducted. This entails combining both independent data sets from the therapist and the child to help define and quantify relationships between the therapist and child during an intervention session. This will help to better explicate causes of change in children's behavior due to specific SIT activities and possible therapist actions. These studies will help guide therapists' activities and their therapeutic use of self during intervention to enhance both behavioral and sensory processing outcomes, and improve overall efficacy of the intervention.

Disclosures: C.M. Holland: None. **E.I. Blanche:** None. **B.L. Thompson:** None.

Poster

034. Autism: Behavioral Analysis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 034.04/C23

Topic: A.07. Developmental Disorders

Support: Intramural Program of the NIMH: ZIA MH002588-26

Title: Dissociations in the neural substrates of language and social functioning in autism

Authors: *J. CRUTCHER[1], M. A. COLLINS[2], A. MARTIN[3], G. L. WALLACE[4]
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Abstract: Impairments in social communication (coupled with intact non-social language skills) are common in children with Autism Spectrum Disorder (ASD). However, there has been far less work examining the language profile and its neural correlates among adolescents and young adults with ASD. Therefore, the current study aimed to address this gap in knowledge.
We recruited adolescents and young adults diagnosed with ASD without intellectual disability (n=30), and typically developing (TD) adolescents and young adults (n=64) matched on age (ASD=21, TD=22), sex ratio (ASD=33% F, TD=22% F), and verbal IQ (ASD=110, TD=116). ASD individuals were diagnosed using DSM-5 criteria. The Communication Checklist Self-Report (CC-SR) is a self-rating scale composed of three scales: Structural Language, Pragmatic Language, and Social Engagement. One high-resolution T1-weighted structural image was obtained from each subject with a magnetization-prepared rapid gradient-echo (MPRAGE) array spatial sensitivity encoding technique (ASSET) sequence. These structural scans were processed using FreeSurfer 5.1 to obtain high-resolution measures of cortical thickness.
We found a main effect of diagnosis, with the ASD group performing worse than the TD group on all three CC-SR scales, and a diagnosis by scale interaction driven by low Social Engagement self-ratings in the ASD group. There were also interactions between the ASD and TD scores on each of the three CC-SR scales and cortical thickness in several regions (Structural: left rostral frontal; Pragmatic: left rostral frontal and right fusiform; Social Engagement: left medial prefrontal). These interactions were driven by higher self-ratings of language/social skills associated with increased cortical thickness in the ASD group, unlike the TD group, which largely showed the inverse (i.e., negative) relationship.
Largely consistent with the literature in children, the ASD adolescents/adults self-rated lower scores in structural and pragmatic language and social functioning than their TD peers. However, ASD scores fell within the average range for both Structural and Pragmatic language (but not Social Engagement) consistent with their average range verbal IQ. There were striking

differences in the neural substrates of language in the ASD and TD groups. Structural and pragmatic language demonstrated shared neural associations in ASD in left inferior frontal regions (consistent with functional imaging studies), while correlations with social behavior were restricted to the left medial prefrontal cortex. These findings suggest dissociations in the neural substrates of language and social functioning in ASD.

Disclosures: **J. Crutcher:** None. **M.A. Collins:** None. **A. Martin:** None. **G.L. Wallace:** None.

Poster

034. Autism: Behavioral Analysis

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Topic: A.07. Developmental Disorders

Support: Conacyt Scholarship No. 576860 (RAV)

Cuerpo Academico de Neurociencias

Cuerpo Academico de Neuroquímica

Title: Improvement of reading and writting skills on autistic children through iPad app training

Authors: ***R. AGUILAR**[1,2], L. GARCIA[1], G. CORIA[1], R. TOLEDO[1], M. HERNANDEZ[1], J. MANZO[1]
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Abstract: Autism is a neurodevelopmental disorder whose features are wide, although social communication skills are impaired in most cases, as well as interests and repetitive behavior. It is therefore that autistic children should be committed to several therapies and enrichment environments which could improve all types of abilities. Previous studies in our lab have shown that virtual stimulation through videogames improve motor, cognitive and social interactions skills on autistic children. Following this line, here we use an iPad app, created especially for the present study in order to improve reading and writing skills on this patients. 10 autistic children from 3 different educational institutions from Xalapa city were exposed to training twice a week, 20 minutes each session until complete 60 sessions. Results showed improvement on reading, writing and recognition of proper name on all subjects; reading, writing and recognition on family names (nuclear family) on 90% of subjects as well as words of body parts, emotions and daily activities such as sleep, eat, shower). These preliminary results allowed us to hypothesize that controlled design and training of virtual teaching tools on screens can lead to improve and develop of reading and writing skills on autistic children.

Disclosures: **R. Aguilar:** None. **L. Garcia:** None. **G. Coria:** None. **R. Toledo:** None. **M. Hernandez:** None. **J. Manzo:** None.

Poster

034. Autism: Behavioral Analysis

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Topic: A.07. Developmental Disorders

Support: IDDRC Pilot Award

Title: Genotype to phenotype correlations in Autism Spectrum Disorder

Authors: M. GOODRICH[1], A. ARMOUR[1], X. YOU[2], K. PANCHAPAKESAN[1], K. DUDLEY[1], C. LUONG-TRAN[1], A. VERBALIS[1], C. SULLIVAN[3], J. DEVANEY[1], S. KNOBLACH[1], A. GUPTA[3], L. ANTHONY[1], *J. CORBIN[1], C. J. VAIDYA[4], L. KENWORTHY[1]
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Abstract: Autism Spectrum Disorder (ASD) comprises a broad spectrum of neurodevelopmental disorders characterized by restricted and repetitive behaviors as well as deficits in social communication and interaction. Currently, diagnosis of ASD relies on clinical behavioral assessments and interviews. Given the lack of biological criteria used in diagnosing and treating individuals with ASD, our group utilized existing genotypic and phenotypic data from children affected by ASD in an effort to correlate specific variants to core ASD behavioral deficits. With a pilot participant pool of 342 individuals, 212 of whom were children affected by ASD, we built a comprehensive dataset comparing genetic and phenotypic profiles for each participant. Saliva samples for each participant were analyzed for allele specific variants in 8 human genes linked to autism-related behavioral deficits, and a battery of neuropsychological testing provided ample behavioral output. With these data, we analyzed relationships between gene variants and scores on tests examining executive function and social communication. Additionally, we assessed existing fMRI data for participants that were scanned to further identify relationships between brain activity and allele variants. Here, we present evidence revealing relationships between phenotype and allele variants for SNPs within the genes *GABRG3/OCA2*, *ADCYAP1R1*, and *NPY*. Furthermore, we present individual gene expression profiles across developmental time from human and mouse brains obtained from data mining of existing databases and our own analyses.

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Poster

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Topic: A.07. Developmental Disorders

Support: Nancy Lurie Marks Family Foundation

New Jersey Governor's Council for Autism Research and Treatments

Title: Nervous systems taxonomy to create new dynamic classification of autism subtypes

Authors: *E. B. TORRES
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Abstract: Current diagnostics systems for autism spectrum disorders rely on observation of behavior for psychiatric (DSM-based) and psychological (ADOS-based) profiling. Such inventories provide static, discrete measures with non-standardized scale and *a priori* enforce statistical criteria under assumptions of normality, linearity and stationarity. While useful in clinical settings, these behavioral criteria have created a rather difficult-to-close gap in basic scientific research. Specifically, this gap exists in the network of knowledge aiming at connecting phenotypic features and genotypic information critical for the development of personalized target therapies within the context of Precision Medicine. Paired to such diagnostic criteria from static-discrete inventories is the lacking of longitudinal outcome measures to dynamically track developmental disorder progression and progression in response to behavioral and pharmacological interventions. In this work, we present a new unifying statistical platform for the individualized behavioral analyses. This platform provides an integrative approach whereby *continuous* physiological data from biorhythms harnessed from multiple areas of the nervous systems aim at closing the gap between behavioral phenotype and genetic profile to further transform static "*one-size-fits-all*" diagnostic model into a model of dynamic diagnoses to capture change and its rate during development and beyond. The new approach is illustrated in the context of ASD whereby we provide classification according to three fundamental classes of nervous systems processes and their cross-talk during natural tasks: *deliberate* (CNS); *spontaneous* (somatic-motor PNS); *inevitable* (autonomic-enteric PNS). By profiling thousands of individuals across different tasks engaging these three classes of processes, we illustrate the new proposed dynamic-classification system based on natural phylogenetically ordered nervous

systems taxonomy. We characterize voluntary, involuntary and autonomic nervous systems biorhythms harnessed in participants with idiopathic ASD, SHANK3-ASD and Fragile-X-ASD in relation to age- and sex-matched controls. Further in a subset of these participants, we show examples of the dynamic, non-linear stochastic nature of the data and its advantageous features for the new classification system. Specific examples of dynamic outcome measures are also provided with uses in the longitudinal tracking of a clinical trial, 30 sessions of occupational-therapeutic interventions and multi-visit-assessment of ASD developmental progression.

Disclosures: E.B. Torres: None.

Poster

034. Autism: Behavioral Analysis

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Support: Nancy Lurie Marks Family Foundation

New Jersey Governor's Council for Autism Research and Treatments

JVJ was partially supported by the NSF 068944-00002B

Title: Computational psychiatry modelling leads to an empirically derived biomarker in an asd clinical trial

Authors: *D. WU[1], E. B. TORRES[2], J. NGUYEN[3], S. MISTRY[4], A. KOLEVZON[5], J. V. JOSE[6,7,8]
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Abstract: Computational psychiatry is promising to connect neuroscience studies to clinical applications. Time-evolving biomarkers with the ability to capture dynamical changes in the nervous system are dearly needed in clinical researches. Along those lines, the combination of computational modeling and empirical data analysis may lead to defining longitudinal biometrics to monitor neurological disorder progression and changes in response to medical interventions. In particular, such models and biometrics would help assess the effectiveness of pharmacological treatments and individualized targeted drug development. In the context of clinical trials related to nervous systems disorders, the ineffectiveness of current assessment metrics in early phases

may lead to risk increase for patients in later phases of the trial. Moreover, given the high heterogeneity that clinical diagnoses give rise to, a *one-size-fits-all* model for clinical trials in any given disorder seems inadequate. Hence, there is a need to introduce objective treatment assessments at an *individualized* level during clinical trials. Here we offer new dynamic biometrics derived statistically from the empirical data, combined with computational psychiatry modelling, to track the outcome of a clinical trial involving Insuline-like Growth Hormone Factor (IGF-1) in children with SHANK3 deletion syndrome and a clinical diagnosis of ASD. Within the context of natural gait movements, we provide a measure of speed smoothness capturing motion signatures of lower body extremities at milliseconds time scales, non-apparent to naked eye detection. Over a period spanning 60 weeks, we show clear transitions in a parameter space derived from minute speed fluctuations in gait kinematics across placebo and drug states. Besides longitudinally tracking the outcome of the trial in children with SHANK3 deletion syndrome, we also compare pre- and post-treatment states with age- and sex-matched controls. We report signature changes towards neurotypical control levels along with individual differences. Our model and empirical results are discussed within the framework of the nascent field of Computational Psychiatry.

Disclosures: **D. Wu:** None. **E.B. Torres:** None. **J. Nguyen:** None. **S. Mistry:** None. **A. Kolevzon:** None. **J.V. Jose:** None.

Poster

034. Autism: Behavioral Analysis

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Program#/Poster#: 034.09/C28

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Support: The New Jersey Governor's Council for Medial Research and Treatment of Autism

Nancy Lurie Marks Family Foundation

The Henry Wallace Foundation

Title: Bridging the gap: An analytical framework for dynamic diagnosis and longitudinal tracking of disorder symptomatology, and intervention outcomes

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Abstract: The NIMH's Research Domain Criteria and the Precision Medicine platform highlight the difficulties in bridging psychiatric and psychological classification methodologies, with

modern biomedical techniques. Variation in approach and precision raise questions over the feasibility of data integration across these areas. Here we provide an overview of two complementary studies combining wearable-sensing technology with clinical diagnostic tools and intervention paradigms, to facilitate a move toward this platform. Through this multi-layered framework, macro-level behavioral outcomes are systematically deconstructed to consider the stochastic signature of biophysical variation at the individual micro-level. Further, drawing on cross-coherence techniques and tenets of graph theory, intrapersonal metrics are considered within the context of self-evolving interpersonal dyadic exchange—a hallmark of the clinician-patient dynamic.
Results are presented from 90 Autism Diagnostic Observation Schedule-2 visits with individuals with idiopathic Autism Spectrum Disorder (N=60), Fragile X (N=10), and a neurotypical control population (N=20)—providing a baseline of un-established normative data for comparison. This framework is extended further via longitudinal tracking and profiling of Occupational and Physical Therapy impact for individuals with Sensory-Processing Disorder (N=5 x 30 Sessions). Analytics demonstrate sensitivity to clinical diagnosis, intervention and axes of symptomatology, as profiled across, and between, sessions. Combined, these studies point to the utility of this framework as a dynamic diagnosis and assessment platform driven by objective data. Further, core clinical tasks and intervention protocols that maximally differentiate individuals are blindly isolated and considered in light of statistically significant variation in underlying biophysical signatures and clinical characteristics. This approach signifies the potential of such methods to enable an objectively informed refinement of clinical batteries and tailored intervention programs. Finally, through the objective dynamic profiling of self-evolving dyadic exchange, ‘transition’ moments are identified, implying levels of interpersonal connection beyond current observational techniques. Overall, results facilitate new dialogue regarding the adoption of a Precision Psychiatry platform for the dynamical diagnosis of neurodevelopmental disorders; provide a novel framework suitable for the M-Health initiative; and culminate in individualized objective outcome metrics sensitive to clinical diagnosis and intervention impact.

Disclosures: **C. Whyatt:** None. **R. Rai:** None. **E.B. Torres:** None.

Poster

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NJ Governor's Council for Autism Research and Treatments

Title: Individualized stochastic characterization of dynamically coupled brain-body biorhythms in ASD vs controls

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Abstract: Autism, a neurodevelopmental disorder defined by difficulties with social cognition, has not been systematically characterized by simultaneous activities of the central and peripheral nervous systems (CNS-PNS). As such, we know very little about the potential contributions of dynamically coupled brain body biorhythms (DCB3) to behaviors present in social exchange. Part of the challenge has been the lack of methodological framework enabling the study of DCB3 in near real-time during natural behaviors. Indeed, most autism studies reflect a top-down approach, thus limiting our ability to uncover possible bottom-up mechanisms, involving autonomic and somatic-motor aspects, and their possible roles in scaffolding central control necessary in social cognition.
Here we offer a unifying statistical platform for individualized behavioral analyses (SPIBA), a new data type (i.e., the micro-movements of DCB3) and a new experimental paradigm to systematically profile and integrate activities harnessed from different levels of the nervous systems during natural behaviors. Specifically, we register electro-encephalography (EEG), bodily kinematics, temperature and heart electrocardiography (ECG) in tandem at 500Hz using wearables among 10 participants naturally walking in 3 modes: (1) (automatic) walking as they normally would; (2) (spontaneous) walking as in (1) with a metronome in the background; (3) (deliberate) walking as in (2) while breathing at a pace set by the metronome. Further, we characterize their involuntary micro-movements during resting state. Thus far, our preliminary findings indicate systemically elevated levels of noise and randomness across all biorhythms under study in 3/3 ASD participants in relation to 8 controls. Most notably, we have found profound statistical differences in the stochastic signatures of heart's inter-beat-interval (IBI) timing of these ASD participants. The disarray in autonomic signatures is also present in their involuntary micro-movements across the body, in their deliberate acts, and in the EEG patterns. While we continue to profile other individuals in the spectrum, we also provide visualization tools to enable real-time monitoring of the unfolding statistical patterns of CNS-PNS interactions during social exchange.

Disclosures: **J. Ryu:** 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.; Nancy Lurie Marks Family Foundation, NJ Governor's Council for Autism Research and Treatments. **E.B. Torres:** 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.; NJ Governor's Council for Autism Research and Treatments, Nancy Lurie Marks Family Foundation.

Poster

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Title: Personalized characterization of longitudinal changes towards typical signatures of gait control in SHANK3 IGF1-clinical trial

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Abstract: Clinical trials have been traditionally tracked under a *one-size-fits-all* statistical model generally using *a priori* imposed assumptions of normality, linearity and stationarity in (*discrete*) subjective data drawn from observational inventories. This approach tends to miss subtle individual changes that may occur at different rates for individuals of different ages and developmental stages. As such, costly and unnecessarily lengthy trials may ultimately halt after phase 3 or 4, owing to subtle cumulative adverse effects in earlier phases of the trial, effects that are not apparent to the naked eye. Likewise, subtle positive gains towards typical patterns may be missed or subsumed under the grand averaging of discrete observational data that tends to smooth out as noise (or altogether miss) important fluctuations inherently present in *continuous* physiological biorhythms. This work introduces a statistical platform and visualization tools for the individualized analyses of natural behaviors of use in Precision Psychiatry. We apply the methods to an interventional clinical trial of Insulin-Like Growth Factor-1 (IGF-1) involving 16 children with SHANK3 deletion syndrome and age- and sex-matched neurotypicals not undergoing the trial. The trial is a randomized cross over design double blind (participant, care provider, investigator and outcome assessor) with two phases (placebo/drug or drug/placebo). We track longitudinal changes in somatic motor patterns across the body in each individual for visits in weeks 0, 12, 16, and 28.
We first establish normative data for each neurotypical representative. Then, we derive fundamental differences in gait behavior at macro-level of kinematics and at micro-level of fluctuations in amplitude and timing of biorhythms' micro-movements during the baseline phase (no drug) comparing SHANK3 and controls. We report the SHANK3 individualized patterns longitudinally evolving during the trial and at the post-trial visit in relation to the baseline normative data. We find transient changes in gait patterns of all SHANK3 participants shifting towards controls above placebo effects that in some children were accompanied as well by

sustained effects throughout the trial and in the post-trial visit. We discuss individual effects and group patterns according to the trial order and potential pharmacodynamics effects in the context of individualized somatic-motor phenotyping for Precision Medicine and Computational Psychiatry.

Disclosures: V. Kalampratsidou: 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.; ancy Lurie Marks Family Foundation, NJ Governor's Council for Autism Research and Treatments. **S. Mistry:** 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.; Nancy Lurie Marks Family Foundation, NJ Governor's Council for Autism Research and Treatments. **A. Kolevzon:** None. **E.B. Torres:** 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.; NJ Governor's Council for Autism Research and Treatments, Nancy Lurie Marks Family Foundation.

Poster

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Title: Brain-behavior relationships in autism spectrum disorder and typical development during an interactive social paradigm

Authors: *T. C. DAY[1], A. NAPLES[1], B. LEWIS[1], K. MCNAUGHTON[1], S.-A. A. CHANG[1], M. J. ROLISON[1], J. A. TRAPANI[1], K. ELLISON[1], E. JARZABEK[1], J. WOLF[1], S. M. MALAK[1], K. STINSON[1], J. H. FOSS-FEIG[2], J. MCPARTLAND[1]
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Abstract: Impairments in eye contact are a core feature of autism spectrum disorder (ASD), yet the relationship between these impairments and brain response during complex social interactions are not well understood. Utilizing gaze-contingent event-related potentials (ERP) during an interactive social paradigm, we aimed to investigate brain-behavior relationships in individuals with ASD and typical development (TD). Relationships among participant gaze behavior, the N170 ERP component, and handedness were explored.
Participants included individuals with ASD (n=122) and TD (n=77) matched on age (5–35 years). ERPs were recorded using 128-channel nets while eye-tracking (ET) was recorded with a remote ET system concurrently. After looking to a crosshair, a face appeared and responded to participant gaze by looking at (direct gaze) or away from (averted gaze) the participant. Gaze (time spent looking at facial features), neural response (N170 amplitude and latency), and handedness (the Edinburgh Inventory) were collected.
The TD group spent more time looking to the left eye [$t(127.6)=-3.0$, $p<.01$], while the ASD group spent more time looking between the eyes [$t(196)=2.4$, $p<.05$]. A main effect of condition emerged [$F(1,111)=4.7$, $p<.05$], with a more negative N170 amplitude to direct gaze across groups. There was a main effect of hemisphere [$F(1,111)=28.0$, $p<.01$], with a more negative N170 amplitude in the right hemisphere, and an interaction between hemisphere and handedness approached significance [$F(1,49)=9.5$, $p=.05$)]. Differences in N170 amplitude between diagnostic groups approached significance [$F(1,111)=3.6$, $p<.10$]. While N170 latency did not differ between groups, decreased right N170 latency was related to increased time spent looking at the left eye ($r=-.21$, $p<.05$) across groups.
Differences in gaze behavior revealed atypical viewing patterns in ASD suggesting individuals may be missing out on key social cues. Neural response to gaze indicated differences in brain processing when presented with direct versus averted gaze. Brain response to face was right lateralized across groups, but a relationship between lateralization and handedness was present, highlighting the importance of considering handedness in the identification social-communicative biomarkers. Differences in brain response between groups approached significance suggesting atypical processing of gaze cues in ASD. Across groups, fixation to the left eye related to more efficient processing. This may have implications for behavior-based therapies; specifically, teaching an individual to look to a specific eye rather than to the eye region may change neural response.

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Poster

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Topic: A.07. Developmental Disorders

Support: University of Florida CTSI Pilot Project Award

APA Dissertation Research Award

Title: Mapping the neural circuitry of restricted repetitive behavior: multimodal neuroimaging in children with autism spectrum disorder

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Abstract: Restricted, repetitive behavior is diagnostic for autism spectrum disorder (ASD) and a prominent feature of other neurodevelopmental disorders. Magnetic resonance imaging has been widely used to study ASD, but relatively few studies have applied multimodal neuroimaging to investigate neural correlates of repetitive behavior. We have obtained a magnetic resonance and diffusion tensor imaging dataset, consisting of children with ASD (n=101) and typically developing (TD) controls (n=106), available through the National Database for Autism Research (NDAR). Measures of restricted, repetitive behavior for children with ASD were also included in this dataset. 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. Moreover, we investigated the relationship between these neuroimaging metrics and clinical assessments of repetitive behavior. Analyses completed to date (N=20) show widespread differences in brain volume in ASD children compared to TD controls, including reduced volumes in the subthalamic nucleus, globus pallidus externa, head of the caudate, nucleus accumbens, internal capsule, corpus callosum, cerebellar cortex, and brainstem. These analyses also showed that in children with ASD, higher repetitive behavior scores from the Autism Diagnostic Interview - Revised were correlated with higher FA in the globus pallidus interna and externa, and lower FA in the striatum. These results extend prior neuroimaging work in ASD, and parallel findings from our lab applying multimodal neuroimaging to an animal model of repetitive behavior.

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Poster

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Topic: A.07. Developmental Disorders

Title: Co-morbid medical conditions, misrecognized pain and disruptive behaviors in individuals with autism spectrum disorder

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Abstract: Background: Impairments in communication can impede the ability of some persons with Autism Spectrum Disorder (ASD) to indicate that they are in pain or reveal the location of their discomfort. These individuals may present with abnormal behaviors, including self-injurious or aggressive behaviors. As a consequence of this, it can be difficult for family members and clinicians to determine an etiology of pain or sometimes even recognize the existence of pain in an individual with ASD. **Case reports**: Patient one is a 12-year-old non-verbal male with ASD who presented with uncharacteristic episodes of violent aggressive behavior, directed primarily toward his mother. The severity of the outbursts necessitated transfer to a hospital emergency department where he was unexpectedly noted to have bilateral otitis media. After antibiotic treatment, he fell asleep and woke up the next morning with no further outbursts. Patient two is a 14-year-old minimally verbal female with ASD who presented to clinic with a several month history of unexplained episodic irritability, disruptive behaviors, and aggressions. She was later referred to a neuroendocrinologist because the behaviors were noted to occur at mid-menstrual cycle. Evaluation found evidence of an imbalance of progesterone and estrogen levels causing dysmenorrhea. The symptoms resolved on correction of the hormonal imbalance. Patient three is a 12-year-old non-verbal female with ASD who presented with a history of an unexplained severe sleep disorder that included difficulty getting to sleep with irritability and aggressive behaviors such as striking out at her parents. Referral to a gastroenterologist resulted in a diagnosis of gastroesophageal reflux disease associated with scarring and ulceration of the esophagus. When treated, all behaviors resolved and no further sleep disruptions occurred. **Conclusion**: We present here three cases of pain in persons with ASD, each of which presented as disruptive behaviors. Individuals with ASD often have one or more co-morbid medical disorders and may present with symptoms that are not easily recognized by primary care physicians or specialists. Rather than seeing disruptive behaviors as a potential

sign of an underlying condition that can cause pain, these behaviors can be interpreted as part of the individual's ASD and be dismissed or treated with psychotropic medications, often with little effect. Clinicians and other caregivers should consider the possibility of a co-morbid medical condition causing pain when presented with changes in behavior, especially in non-verbal and hypo-verbal individuals with ASD.

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Poster

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Title: Narrower attentional filters explain enhanced motion perception in autism spectrum disorder

Authors: *S. O. MURRAY[1], M.-P. SCHALLMO[1], A. KALE[1], R. BERNIER[2]
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Abstract: Recent efforts to identify underlying neuro-computational changes in autism spectrum disorder (ASD) have targeted sensory and perceptual systems as they feature prominently in symptomatology, are amenable to comprehensive psychophysical measurement, can be directly tied to electrophysiological findings in animals, and can be modeled using well-established principles of cortical computation. For example, large enhancements in visual motion discrimination found in ASD compared to controls (Foss-Feig et al., 2013) were recently described as a deficit in "normalization" (Rosenberg et al., 2015) – a computation that reflects an interaction between excitatory and suppressive neural processes in the brain (Carandini & Heeger, 2012). Weaker normalization would result in larger amplitude neural responses and potentially enhance behavioral performance in tasks that depend on neural sensitivity such as motion discrimination. A challenge of this approach, however, is that changes in perceptual performance – even when they appear "low level" such as in visual motion processing – are highly susceptible to differences in attentional mechanisms.
Here we demonstrate how narrower attentional filters – in the absence of any explicit experimental manipulation of attention – can provide the most comprehensive and parsimonious explanation for previously observed enhancements in motion perception in ASD. We first

replicate the previous experimental finding demonstrating enhanced motion perception in ASD in a group of 17 adults diagnosed with ASD compared to neurotypical (NT) controls. Specifically, individuals with ASD had shorter motion duration thresholds for high-contrast gratings of all stimulus sizes, whereas at low contrast the ASD group outperformed the NT group only for large stimuli. We then show why weakened normalization cannot fully explain the mixed effects of contrast and size and how the hypothesis fails to generalize to other psychophysical measurements, such as visual contrast detection. Next, we demonstrate how a version of the normalization model (Reynolds & Heeger, 2009) that incorporates narrower attentional spatial filters can account for the full range of performance differences across size and contrast in the task. Our model is consistent with recent empirical findings showing that individuals with ASD have a sharper spatial gradient of attention (Robertson et al., 2013). Finally, we demonstrate how variability in attentional filter width across individuals with ASD can potentially explain the apparent enhancements, deficits, and null findings in the literature related to sensory processing in this disorder.

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Poster

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Title: Reduced sensory habituation in autism

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Abstract: Habituation involves reduction of neural and behavioral response over the presentation of repeated, predictable stimuli. Based on our recent theoretical account of autism as a disorder of prediction, we hypothesize that autism spectrum disorder (ASD) may be associated with reduced habituation. To investigate whether habituation is indeed reduced in autism, EEG data were recorded from neurotypical (NT) and autistic children during 300 trials of repeated auditory tone bursts and visual input in two experiments. ERPs were calculated for each subject in 50 trial segments using a sliding window over all trials. We calculated the line of best fit across successive potentials (amplitude) of the most prominent ERP peak using the least square method. Slopes of the best fit line for each subject were used to determine the overall change in stimulus-induced activation. Fig. 1A shows sample ERP peaks and the best-fit line from 1 NT

and 1 ASD in response to auditory tones. NT participant shows gradual reduction in ERP amplitude over time (negative slope), while the ASD participant shows a slight increase (positive slope). The upper right bar-plot shows the habituation slopes of individual ASD (N=6) and NT (N=8) participants, who exhibit pronounced habituation, in contrast to those with ASD. The group average results are inset. Fig 1B shows the same evoked potential response and slope analysis for the visual experiment (NT=8, ASD=5). We find significant differences ($p<0.05$) in habituation profiles between our ASD and NT groups for both the auditory and visual experiments. ASDs show reduced habituation as indicated by positive or less negative slopes compared to NTs. The data support the hypothesis that autism is associated with reduced habituation to sensory stimuli and may help explain commonly observed features of ASD: sensory hypersensitivities (aversion to stimuli with negative valence) as well as restricted and repetitive interests (sustained engagement with positive valence stimuli). Furthermore, these results provide support for the broader hypothesis of impaired prediction in autism.

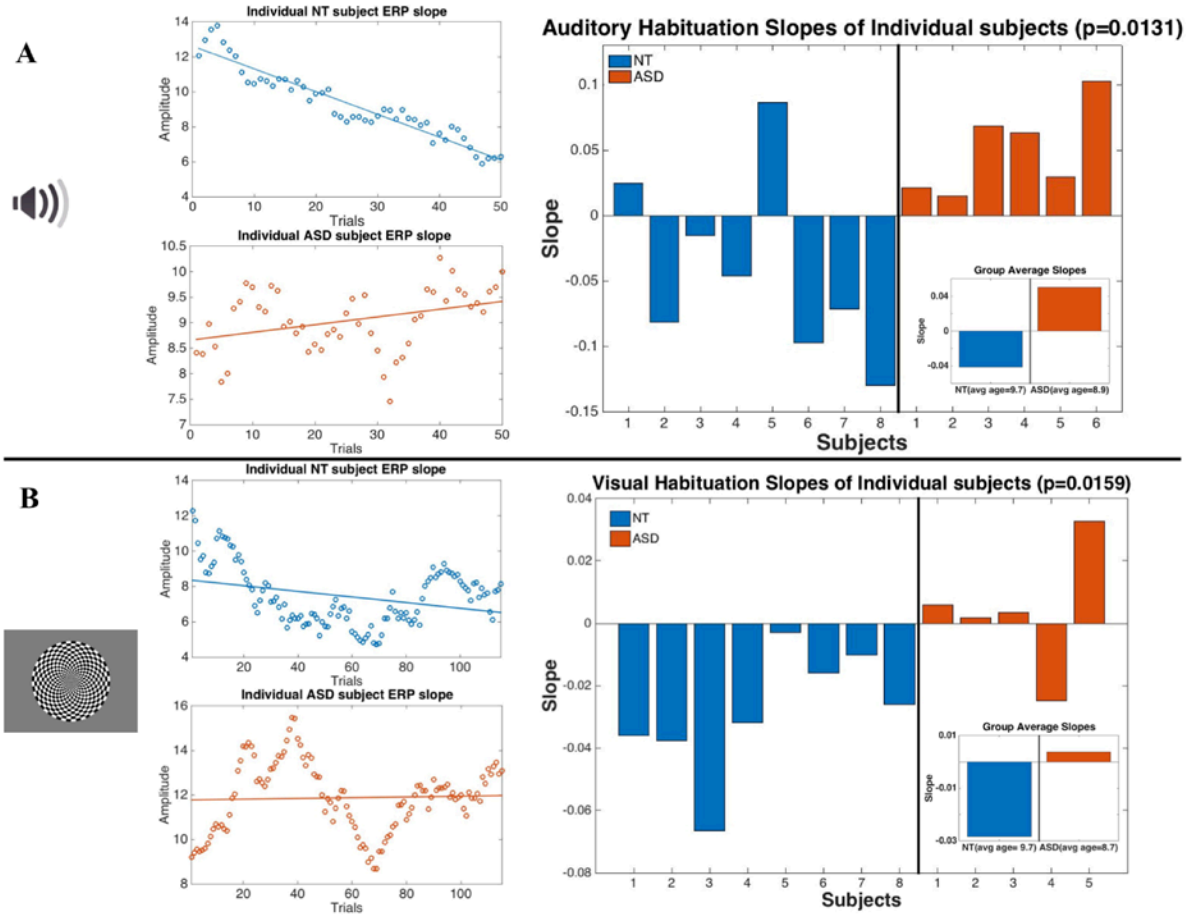

Figure 1. Auditory and Visual Habituation Results

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Topic: A.07. Developmental Disorders

Support: Nancy Lurie Marks Family Foundation

New Jersey Governor's Council for Autism Research and Treatments

Title: Neonatal biomarker of healthy growth, neuromotor control and motor coordination

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Abstract: Current rises in neurodevelopmental disorders (e.g. Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, etc.) call for early detection of neurodevelopmental derail. At an early stage of life it is not possible to clinically diagnose a given categorical disorder (e.g. defined by DSM criteria or by other inventories/questionnaires like the ADOS, ADI, etc.) However, detecting early deviations from normative data signaling neurodevelopmental derail early can help parents and pediatricians intervene with proper medical and therapeutic means to help the peripheral nervous systems connect to the central nervous systems; stimulate healthy growth and overall development. This in turn can help the neonate gain bodily autonomy, coordination and somatic-motor control. Keeping those goals in mind, new methods for the dynamic tracking of longitudinal neurodevelopment seem critical for the tracking of change and the early detection of risk for a neurodevelopmental disorder. Along those lines, recent works from our labs have initiated avenues to develop new methods for mobile Health amenable for parents and pediatricians to use commercially available non-invasive means to track healthy neonatal development. This work has uncovered new outcome measures of healthy somatic-motor development and physical growth in 36 babies (24 control CT babies, born full-term without complications vs. 12 pre-term born at risk AR, with complications). We combine these data from leg motions with arm motion data from additional 25 CT babies and 12 AR babies to introduce a new dynamic biomarker of arm and leg coordination. These biometrics were empirically derived from longitudinally tracking the babies for 4-5 months over 5 visits starting at least at 2 months of age. We identify risk as early as the first visit and show consistent stunting in neurodevelopmental progression, acquisition of coordination and physical growth for a set of the babies in contrast to healthy signatures. By providing normative data for healthy neuromotor development, arm and leg coordination and physical growth we establish important dynamic diagnostics axes useful to detect rather early deviations from neurotypical patterns and predict risk forecasting developmental disorder of the

nascent nervous systems. We discuss our results in the context of Precision Medicine and Computational Pediatrics.

Disclosures: **J. Vero:** Other; Rutgers Biomedical Engineering Department, Rutgers Psychology and Cognitive Science Department, University of South California. **B.A. Smith:** None. **E.B. Torres:** A. Employment/Salary (full or part-time):; Rutgers University Psychology and Cognitive Science Departments.

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Title: Biomarkers of co-morbid anxiety and depression in Autism Spectrum Disorders

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Abstract: Autism Spectrum Disorders (ASD) are highly co-morbid with anxiety and depression and establishing biomarkers of these co-morbidities can lead to both treatment and diagnostic advances. In the current study, we examine serum markers of inflammation (C-reactive protein and interleukins), whole blood (WB) levels of serotonin, and (1)H-MRS measures of metabolite levels in brain and correlate these with measures of anxiety and depression and social functioning in adults diagnosed with ASD between the ages of 18 and 30. Diagnosis and Intelligence Quotient was confirmed with staff administered Autism Diagnostic Observation Schedule, 2nd ed., (ADOS-2). Clinical assessments included; Structured Clinical Interview for DSM-IV, (SCID), Kaufman Brief Intelligence Test, 2nd ed., (KBIT-2), Beck Depressive Inventory (BDI-II), Rumination Response Scale (RRS), and Social Response Scale (SRS). (1)H-MRS data were acquired with 3T scanner. Results showed a wide range of anxiety and depressive symptoms with IQ correlating with anxiety (R^2 =.60). Individuals with lower levels of WB serotonin reported significantly more severe social anxiety and social anhedonia scores (F = 2.88, p = .008). (1)H-MRS data showed lower N-acetylaspartate (NAA) correlated with higher levels of C-reactive protein (R^2 = .95) and more severe social functioning and social anhedonia (R^2 = .96). Consistent with animal studies, high levels of choline (Cho) correlated with high levels of WB serotonin (R^2 = .94) and lower levels of choline correlated with more severe depressive symptoms (R^2 = .99).Our results indicate that biological substrates such as inflammatory markers and the serotonergic neurotransmitter system are linked to anxiety and depressive systems in ASD. MRS metabolites such as NAA and Cho involved in neuronal health

are also shown to be related to inflammatory markers and serotonergic neurotransmitters as well as clinical affective symptoms.

Disclosures: H. Garman: None. **P. Whitaker-Azmitia:** None. **K. Gadow:** None.

Poster

034. Autism: Behavioral Analysis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 034.19/C38

Topic: A.07. Developmental Disorders

Title: Cortical thickness correlates of subclinical autistic traits in young adulthood

Authors: *E. RICHARD[1], C. S. PENG[1], E. MEHTA[1], C. YAO[1], B. TRIVEDI[1], G. L. WALLACE[1], A. R. KNODT[2], A. HARIRI[2]
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Abstract: Studies of neural foundations of Autism Spectrum Disorder (ASD) face challenges involving heterogeneity within the disorder and often-small sample sizes. Because traits associated with ASD can be viewed continuously and extend to the general population, we can seek to identify structural neural endophenotypes of ASD in large and relatively unconfounded (no comorbidities) subclinical samples to observe unobscured links between ASD-related behavior and cortical structure.
Data Selection: The current study included 382 (152 male) 18-22-year-old adults who completed self-ratings of autistic traits using the three-factor (Sociability, Mentalizing, Detail Orientation; Palmer et al., 2015) Autism-Spectrum Quotient (AQ). Participants also provided one structural magnetic resonance imaging scan. The CIVET brain-imaging pipeline (v2.0) and the SurfStat image analysis suite were used to derive vertex-level cortical thickness (CT) values and complete analyses.
Data Analysis: There were significant main effects for total AQ score and all AQ subscales (FWE corrected *p*s<.05). Total AQ score was positively correlated with CT in the right motor cortex. The Sociability subscale score was negatively correlated with CT in the right insula/orbitofrontal cortex. There were positive correlations between the Mentalizing subscale score and both bilateral insula and right inferior frontal cortices, and between the Detail Orientation subscale score and bilateral primary motor and left superior frontal cortices.
Conclusions: Strikingly, the most robust associations between ASD traits and cortical structure were found at the subscale level of the AQ, rather than utilizing the global score. This suggests dissociations in the relationship between social vs. nonsocial autistic traits and cortical structure. Indeed, both the insula and right inferior frontal cortex were associated with autistic social traits, which jibes with a large functional imaging literature implicating these regions as neural

substrates of social-emotional behavior. Left hemispheric involvement in Detail Orientation corroborates both neuropsychological and functional imaging studies of locally-oriented processing. Taken together, these results suggest brain-based dissociations of social and non-social autistic traits, which inform future avenues to pursue in exploring neural endophenotypes of ASD.

Disclosures: E. Richard: None. **C.S. Peng:** None. **E. Mehta:** None. **C. Yao:** None. **B. Trivedi:** None. **G.L. Wallace:** None. **A.R. Knodt:** None. **A. Hariri:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.01/C39

Topic: A.07. Developmental Disorders

Support: Jim and Betty Ann Rodgers Chair Fund

The Escher Fund for Autism

Title: Transgenerational transmission of reversal learning deficits in a mouse model of paternal nicotine exposure

Authors: *D. M. MCCARTHY, M. J. WILLIAMSON, P. G. BHIDE
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Abstract: We developed a paternal nicotine exposure mouse model in which adult male mice were exposed to nicotine (200µg/ml) in drinking water for 12 weeks. While the nicotine exposure was ongoing, the mice were bred with naïve females. We found that the offspring of the nicotine-exposed fathers displayed hyperactivity and inattention, phenotypes commonly associated with ADHD. Another phenotype associated with ADHD is cognitive inflexibility. It is also a core symptom of autism spectrum disorder. Cognitive flexibility is the ability to seamlessly switch from one mental task to another while the rules of the previously learned task are changed. Reversal learning is a behavioral measure of cognitive flexibility. We analyzed reversal learning in the paternally nicotine-exposed mice using a modified Barnes maze. The mice are initially trained to avoid a stressful environment by escaping into an assigned escape hole in the maze. Next, on the day of reversal, the escape hole is moved to a new location. Male and female mice from nicotine-exposed fathers made significantly greater number of errors before successfully locating the new escape hole. The male mice also took significantly longer time to find the new escape hole. These data show that paternal nicotine exposure produces significant reversal learning deficits (i.e. cognitive inflexibility). In other experiments, we found a significant increase in methylation of DNA of the spermatozoa of the nicotine exposed fathers,

suggesting that nicotine induced epigenetic modification of the fathers' germline is associated with development of the behavioral phenotypes in the offspring.

Disclosures: D.M. McCarthy: None. **M.J. Williamson:** None. **P.G. Bhide:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.02/C40

Topic: A.07. Developmental Disorders

Title: Prenatal nicotine exposure may induce immune activation of the kynurenine pathway in the cerebellum

Authors: *R. B. BASSEY, H. WANG, M. C. GONDRE-LEWIS
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Abstract: Despite many public health programs in the United States promoting the risks of smoking while pregnant, only 25% of women who smoke quit during pregnancy. Prenatal drug exposure is therefore a significant public health concern linked to behavioral problems such as attention-deficit/hyperactivity disorder (ADHD), depression and anxiety in the offspring. Nicotine is thought to be the main neuroteratogen, and can easily penetrate blood-placenta barrier to interact with functional nicotinic acetylcholine receptors (nAChRs) in the fetal brain. nAChRs are detected in various regions of the human brain, including the cerebellum, and play an important role in many aspects of neurological development. Prenatal nicotine exposure is believed to disrupt the timing of the actions of acetylcholine, by binding to nAChRs prematurely, resulting in dysfunction of numerous pathways and systems within the central nervous system. The widely accepted, classical function of the cerebellum is primarily associated to movement, gait, posture, and balance, but its possible involvement in cognition, emotion processing and behavior has recently been suggested. The cerebellum may be altered in many psychiatric disorders, including schizophrenia, bipolar disorder, unipolar depression, anxiety, and attention deficit hyperactivity disorder; and is possibly related to a range of psychopathological manifestations. The kynurenine pathway, a major pathway of tryptophan catabolism, contributes to several important biological processes and its activation in response to inflammatory conditions, such as stress, has been implicated in several neurodegenerative diseases, inflammation, and depression. We hypothesize a possible immune activation of the kynurenine pathway in the cerebellum in response to prenatal nicotine exposure. To test our hypothesis, pregnant dams were administered nicotine using an osmotic pump. The offspring were euthanized at postnatal days 1 (P1), P14 and P70 and each cerebellum harvested and processed. We then determined, using western blot, the expression of Indoleamine 2,3-dioxygenase (IDO) and Tryptophan 2,3-dioxygenase (TDO) - enzymes that convert tryptophan to kynurenine. Our

data suggests a possible modulated expression of IDO and TDO in the rats exposed to nicotine prenatally compared to control. This suggests that prenatal nicotine exposure may activate the kynurenine pathway, resulting in accumulation of its neurotoxic metabolites downstream. Deciphering the precise interaction of kynurenine with cerebellar mediated behaviors is intriguing and could provide novel perspectives in analyzing the pathogenesis of early life stress.

Disclosures: R.B. Bassey: None. **H. Wang:** None. **M.C. Gondre-Lewis:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.03/C41

Topic: A.07. Developmental Disorders

Support: GW Program for Pediatric Dysphagia (P01HD083157)

Title: Modification of pediatric dysphagia by altering maternal Vitamin A intake

Authors: *G. BANYAI[1], J. SABATINO[3], A. S. LAMANTIA[3], T. M. MAYNARD[4], I. ZOHN[2]
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Abstract: Pediatric dysphagia—disrupted feeding and swallowing—affects a high proportion of children with developmental disorders and virtually all children with 22q11.2 Deletion Syndrome (22q11DS). Normal feeding and swallowing relies upon precise coordination of oral, lingual, palatal, laryngeal and esophageal structures controlled by motor commands and sensory feedback from cranial nerves and hindbrain circuits. Our group recently established the first mouse model of pediatric dysphagia. Thus we can evaluate cellular, molecular, and developmental mechanisms underlying this disorder. Moreover, our analysis can include both craniofacial and neural circuit disruptions that may interact to increase severity of pediatric dysphagia in 22q11DS. In the *LgDel* 22q11DS mouse model, we found that altered retinoic acid (RA)-dependent hindbrain patterning leads to cranial nerve (CN) and craniofacial dysmorphogenesis that prefigures feeding and swallowing difficulties. These phenotypes parallel those associated with Vitamin A (dietary metabolic precursor of RA) teratogenicity due to altered maternal intake. Based upon varying maternal dietary intake of Vitamin A, we find that mid-gestation *LgDel* embryos (Embryonic day 10.5) are sensitive to small changes in Vitamin A exposure that are inconsequenetial for WT littermates. To test the hypothesis that altering maternal Vitamin A intake modifies the frequency and severity of developmental disruption associated with pediatric dysphagia, *LgDel* embryos were exposed to distinct Vitamin A levels through modification of maternal diet throughout pregnancy. E10.5 embryos were dissected and

CNs visualized in whole mount samples. *LgDel* and WT embryos exposed to distinct Vitamin A levels via mothers on each diet were scored for CN phenotypic frequency and severity. We find that abnormal development of CN-V, CN-IX and CN-X is aggravated beyond the level seen in *LgDel* embryos whose mothers consume diets with non-teratgenic levels of Vitamin A; in contrast, these changes in Vitamin A exposed WT littermate embryos have no consequence for CN development. Apparently, the *LgDel* embryo has reduced capacity to buffer small changes in Vitamin A exposure, providing a novel mechanism to explain the varied frequency and severity of many 22q11DS phenotypes including dysphagia.

Disclosures: G. Banyai: None. **J. Sabatino:** None. **A.S. Lamantia:** None. **T.M. Maynard:** None. **I. Zohn:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.04/C42

Topic: A.07. Developmental Disorders

Title: The role of brain stem 5HT1A and GABA-A receptors in the thermoregulatory response to hypoxic stress

Authors: *A. L. SCHMIDT, J. BROWN, R. POWELL, L. NELSON, S. HETRICK
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Sudden Infant Death Syndrome (SIDS) is a leading cause of infant mortality. Alterations in brainstem development of Serotonin (5HT) and GABA are linked to its cause. The sympathetic premotor neurons located in the Nucleus of the Raphe mediate protective cardiovascular responses to environmental stress. It is hypothesized that alteration in these receptors at the NRP will also impair protective thermoregulatory responses to hypoxic stress such as hypothermia. Using aseptic techniques, male and female Sprague-Dawley rats (225-325g) were instrumented with radiotelemetry probes to non-invasively measure core temperature (Tc). Using a stereotaxic device, a steel cannula was inserted into the brainstem allowing microinjection at the NRP. After recovery (1 week), rats were housed in a thermal gradient which allowed them to select their ambient temperature (STa) and thereby facilitated behavioral thermoregulation. Once acclimated to the gradient and to handling, 30mM of either a 5HT1A agonist (8OH-DPAT or “DPAT”), antagonist (WAY100635), a GABAA agonist (Muscimol), antagonist (Bicuculine) or ACSF (control vehicle) was then microinjected into the NRP immediately before exposure to 6% O2 for 60 min. In rats injected with ACSF, Tc decreased by 1.8° C while the Tc of those injected with DPAT and WAY decreased by 3.8° C and 2.8° C respectively. Those injected with Muscimol and Bicuculine exhibited similar hypothermic responses to control in that the Tc dropped by 2.0° C and 1.9° C respectively. There were mild

decreases in STa of control group rats (4.3° C) which was exacerbated in DPAT injected rats (8° C). Importantly, the STa responses to hypoxic stress helped facilitate Tc changes suggesting coordination between behavioral and autonomic thermoregulatory mechanisms which facilitated the protective hypothermic response. Rats injected with WAY seemed to reverse this trend initially with an increase in STa (3°C) which quickly faded. Muscimol and Bicuculine seemed to have minimal effect on STa responses. These preliminary data suggests that GABA-A receptors have minimal role in the thermoregulatory response to hypoxic stress. However, activation of the inhibitory 5HT1A receptor exacerbates the hypothermic response to hypoxic stress and may facilitate this protective response. Alterations in 5HT neuronal development may cause inadequate behavioral (STa decrease) and autonomic (Tc decrease) heat loss responses to hypoxic stress and may be a significant factor in the etiology of SIDS.

Disclosures: A.L. Schmidt: None. **J. Brown:** None. **R. Powell:** None. **L. Nelson:** None. **S. Hetrick:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.05/C43

Topic: A.07. Developmental Disorders

Title: Developmental hyperserotonemia induced purkinje cell loss, implications in autism

Authors: *L. HOUGH[1], A. W. BANDELOW[2], M. L. BEKAS[3], K. HILL[3]
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Abstract: Neuropathological changes to the cerebellum have been implicated in Autism Spectrum Disorder (ASD) and have been increasingly linked to behavioral expressions characteristic of the condition. The cerebellum is essential for many, if not most, of the processes that are perturbed in autism including language and communication, social interactions, stereotyped behavior, motor activity and motor coordination, and higher cognitive functions. As such, investigations into factors which may affect the development of cerebellar circuitry are vital to our understanding of the disorder. Elevated blood serotonin in perinatal development (Developmental Hyperserotonemia) is the most consistent neurochemical finding reported in ASD, and has been implicated in the pathogenesis of the disorder. Accordingly, pre-and postnatal administration of the non-selective serotonin agonist, 5-methoxytptamine (5-MT), has been hypothesized as a model of developmental hyperserotonemia (DHS) to investigate the behavioral and morphological implications in ASD. Our previous studies, examining the effects of DHS, found significant neurodevelopmental changes in the architecture and connectivity of neurons in the dentate nucleus of the cerebellum and the thalamic nuclei. The present investigation has shown alterations in the development of Purkinje cells in the posterior

cerebellum of DHS rats. Using unbiased stereological techniques, serial sections of DHS rats were compared to age-matched controls, specifically analyzing the effects of treatment on cellular volume, and estimated cell number, area, and distribution within the posterior lobe of the cerebellum. Significant decreases in Purkinje cell numbers were estimated, with a decrease in soma size, and expression of the calcium binding protein calbindin (CB) significantly reduced. Significant changes to Purkinje cell dendritic arbors were also recorded as shorter and less complex when compared to controls. These results suggest that DHS induces significant changes to cerebellar development and is an effective animal model to study the cerebellar alterations in ASD.

Disclosures: L. Hough: None. **A.W. Bandelow:** None. **M.L. Bekas:** None. **K. Hill:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.06/C44

Topic: A.07. Developmental Disorders

Title: Effect of extreme prematurity on brain monoamine metabolism

Authors: *S. SEO[1], S. E. KOHE[1], E. GOWING[1], Y. ZHENG[2], I. KOKAY[1], D. R. GRATTAN[1], P. LIU[1], D. E. OORSCHOT[1]
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Abstract: Children born extremely prematurely can experience repeated hypoxic injury to the brain. They can also develop hyperactivity that is attention deficit hyperactivity disorder (ADHD)-like, as well as impulsivity. Males are more vulnerable. In a new Sprague-Dawley rat model of repeated hypoxic brain injury during the equivalent of extreme prematurity, ADHD-like hyperactivity and impulsivity were observed in males but not females. Based on the literature, we hypothesized in this study that: (i) ADHD-like hyperactivity in males may be due to cerebral deficits in the metabolism of dopamine and/or noradrenaline and (ii) impulsivity may be due to cerebral deficits in the metabolism of serotonin. In the first cohort of animals, these monoamines and their metabolites were investigated in the striatum and prefrontal cortex of repeated hypoxic (11 males, 6 females) and repeated normoxic (8 males, 5 females) rats using high performance liquid chromatography coupled to an electrochemical detector. This comparison was undertaken in 7-month-old rats after testing for ADHD-like hyperactivity and impulsivity from 2 months-of-age. In the repeated hypoxic male rats, we observed ADHD-like hyperactivity and impulsivity. We also observed a significant decrease in the concentration of the dopamine metabolite 3-4-dihydroxyphenylacetic acid (DOPAC) and in the DOPAC/dopamine ratio in the right prefrontal cortex, and a significant increase in serotonin concentration in the right posterior striatum, compared to control repeated normoxic rats. No differences were

observed in the female rats. These results supported our hypotheses. In a second cohort of animals, the concentrations of noradrenaline and its metabolite vanillylmandelic acid (VMA), and of the dopamine metabolite homovanillic acid (HVA), were compared in the rat striatum and prefrontal cortex at postnatal day 50 for repeated hypoxic (8 males, 7 females) and repeated normoxic (6 males, 6 females) rats. We observed no changes in the concentration of noradrenaline and its metabolite VMA for both sexes when the respective repeated normoxic and repeated hypoxic animals were compared. In the females there was a decreased concentration of HVA in the right anterior striatum, and in the right posterior striatum, in the repeated hypoxic group compared with repeated normoxic animals. These results suggest that ADHD-like hyperactivity in males is not associated with the concentration of noradrenaline nor VMA in the striatum and prefrontal cortex. The HVA changes detected in the female repeated hypoxic brain may contribute to behaviors that are not related to ADHD-like hyperactivity.

Disclosures: S. Seo: None. **S.E. Kohe:** None. **E. Gowing:** None. **Y. Zheng:** None. **I. Kokay:** None. **D.R. Grattan:** None. **P. Liu:** None. **D.E. Oorschot:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.07/C45

Topic: A.07. Developmental Disorders

Title: Effects of sex, age and maternal immune stimulation on dopamine receptors

Authors: *A. BIEGON[1], S. HOROVITZ-PERY[2], J. DHAWAN[1], I. WEINER[2]
[1]Neurol., Stony Brook Univ., Stony Brook, NY; [2]Psychology, Tel Aviv Univ., Tel Aviv, Israel

Abstract: Infections during pregnancy are known to increase the risk of schizophrenia in offspring. Consequently, maternal immune activation is used as a neurodevelopmental animal model of schizophrenia; demonstrating sex differences in age of onset reminiscent of those documented in humans. Dopamine receptor density and function are deranged in schizophrenia and are targeted by antipsychotic agents. We hypothesized that maternal immune activation in rats affects dopamine receptor density in an age, sex and region dependent manner. To test this hypothesis, pregnant rats were injected on gestational day 15 with saline or the viral mimic polyriboinosinic-polyribocytidylic acid (poly I:C). Brains of male and female offspring (N=5/sex/age/treatment) killed on postnatal days 34, 48 or 95 were cryosectioned and processed for quantitative autoradiography of dopamine D1 using the radioligand [^{3}H]SCH23390. In adult male offspring, prenatal poly-I:C was associated with significantly decreased D1 receptor density in the frontal cortex, substantial nigra and peri-rhinal cortex. This effect was not observed in females, although both sexes exhibit schizophrenia-like behaviors at this age. but not females. Increased D1 density was also observed in 48day old male but not female offspring; before

eruption of behavioral changes. There was also no effect of poly I:C on male or female adolescent rats (34 day old), however both groups (poly I;C and vehicle) demonstrated a large and statistically significant sex difference in D1 receptor density in the hippocampus. D1 receptor density in male hippocampus was 2-fold higher relative to females. These results demonstrate a sex-dependent developmental trajectory for dopamine D1 receptors and a sexually divergent response to maternal immune activation, which may explain, at least in part, the sex differences in brain structure and behavior observed in this animal model and in schizophrenia.

Disclosures: A. Biegon: None. **S. Horovitz-Pery:** None. **J. Dhawan:** None. **I. Weiner:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.08/C46

Topic: A.07. Developmental Disorders

Support: Institutional Start-up funds

Title: Characterization and localization of tyrosine hydroxylase-labeled neurons in the ventral midbrain during embryonic development of the gray short-tailed opossum (Monodelphis domestica)

Authors: A. C. CAMACHO[1], H. FILIZOLA[2], *M. GIL[3,1], J. L. VANDEBERG[4,5], G. A. DE ERAUSQUIN[6,1]
[1]Sch. of Med. Dept. of Biomed. Sciences, Div. of Neurosciences, [2]Dept. of Hlth. and Biomed. Sci., [3]Dept. of Psychological Sci., [4]South Texas Diabetes and Obesity Inst., [5]Sch. of Med. Dept. of Biomed. Sci., The Univ. of Texas Rio Grande Valley, Brownsville, TX; [6]Sch. of Med. Dept. of Neurol. and Psychiatry, The Univ. of Texas Rio Grande Valley, Harlingen, TX

Abstract: The gray short-tailed opossum, *Monodelphis domestica*, is a marsupial whose offspring is born at very early developmental stages. *Monodelphis* neonates approximate the development of a six-week old human embryo and 12.5 days-old mouse embryo, and the rest of gestation occurs outside the mother. Thus, the *Monodelphis* is an excellent model for investigating high-risk events during embryonic development that can lead to disorders like schizophrenia in adults. Our laboratory focuses on characterizing and describing the regional distribution of dopaminergic neurons in the *Monodelphis* brain, with a special focus on the ventral midbrain. Dopaminergic neurons (DN) in the midbrain project to a number of forebrain areas, and dysfunction of these pathways is linked to disorders like schizophrenia and Parkinson's disease. Therefore, we developed a protocol to produce primary cultures from the mesencephalon. The cell cultures were developed using tissue from zero- to one-day old post-natal (PN) pups. With the use of immunocytochemistry we studied the expression of tyrosine

hydroxylase (TH), a widespread marker for DN, along with microtubule associated protein 2 (MAP2) and a neuronal marker (NeuN-Fox3) at different ages of the PN development of the cultured neurons. We found that staining of TH and MAP2 was present in all stages studied in the *Monodelphis* neurons. We also used immunohistochemistry to study the presence and localization of TH, MAP2 and NeuN during different stages of the neurodevelopment of *Monodelphis* embryos. These findings will be the foundation to study environmental risk factors, such as Influenza virus infections, that are linked to schizophrenia pathogenesis.

Disclosures: A.C. Camacho: None. **H. Filizola:** None. **M. Gil:** None. **J.L. VandeBerg:** None. **G.A. De Erausquin:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.09/C47

Topic: A.07. Developmental Disorders

Support: Support from The Autism Research Foundation

Support from The Wallace Research Foundation

Title: GABA and Dopamine receptor involvement in sensorimotor gating in the rat model: An autoradiography study

Authors: *M. FAZAL[1], E. T. CHOW[1], C. R. CLANCY[1], J. SKEFOS[1], E. D. LEVIN[2], M. L. BAUMAN[1]
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Abstract: Sensorimotor gating is the process of screening out irrelevant internal and external stimuli to allocate neural resources for salient information. Behaviorally, sensorimotor gating can be gauged by measuring pre-pulse inhibition (PPI), an index of startle response suppression to a strong sensory stimulus (e.g. 110 dB acoustic pulse) when preceded by a weaker sensory stimulus (e.g. 68-77 dB acoustic prepulse). Sensorimotor gating is impaired in a number of neurological disorders, such as autism spectrum disorders, sensory processing disorders, and schizophrenia. The neural circuitry underlying PPI has been shown to include dopaminergic, GABAergic, cholinergic and histaminergic systems. Our prior work in a rat model explored the role of cholinergic/histaminergic systems in PPI. Using the NMDA glutamate receptor antagonist dizocilpine, we induced PPI impairment, and subsequently reversed this PPI impairment using the histamine H1 receptor antagonist pyrilamine. In the present autoradiographic study, we extend these findings by exploring potential GABAergic and dopaminergic (D2) involvement in

PPI disruption induced by administration of dizocilpine, as well as PPI improvement induced by treatment with pyrilamine. We have investigated group level differences in receptor binding in the basolateral amygdala (BLA), hippocampus (areas CA1, CA3, and dentate gyrus), and striatum. There were four treatment groups: control animals (n=9) were administered saline, and treatment animals were administered either dizocilpine (n=9), pyrilamine (n=9), or a combination of dizocilpine and pyrilamine (n=9) for 4 weeks. Specific binding of the GABA-B and D2 receptors was determined using [3H] CGP54626 and [3H] YM- 09151-2, respectively. Preliminary results have found no differences in GABA-B receptor binding density between the PPI impaired treatment groups with and without pyrilamine in the BLA, hippocampus, and striatum. However, GABA-B receptor density was significantly decreased in dizocilpine exposed groups in the BLA ($p=0.04$), CA1 ($p<0.0001$), CA3 ($p=0.014$), and dentate gyrus ($p<0.0001$). Our D2 experiments are currently underway and will be completed within the next few months. GABA-B receptors in these brain regions may play a mechanistic role in dizocilpine's effect on PPI. Further studies to further confirm the role of GABA in PPI impairment and recovery are ongoing. In addition, our results on the involvement of dopamine in regulation of the PPI circuitry could provide an alternative approach to treating diseases where such PPI impairment is widely reported.

Disclosures: **M. Fazal:** None. **E.T. Chow:** None. **C.R. Clancy:** None. **J. Skefos:** None. **E.D. Levin:** None. **M.L. Bauman:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.10/C48

Topic: A.07. Developmental Disorders

Support: FDA Grant E0752801

Title: Cyclosporine exacerbates ketamine toxicity in zebrafish

Authors: *J. KANUNGO[1], M. DUMAS[2], S. F. ALI[3], M. G. PAULE[4], Q. GU[5], B. ROBINSON[6]
[1]Neurotoxicology, Natl. Ctr. For Toxicological Research/Food and Drug Admin., Jefferson, AR; [2]Natl. Ctr. for Toxicological Res., Jefferson, AR; [3]Neurochemistry Lab, Div. of Neurotoxicology, Natl. Ctr. Toxicological Res/Fda, Jefferson, AR; [4]Div. of Neurotoxicology, FDA's Natl. Ctr. For Toxicological Res., Jefferson, AR; [5]FDA Natl. Ctr. for Toxicological Res., Jefferson, AR; [6]Neurotoxicology, Natl. Ctr. For Toxicological Res., Jefferson, AR

Abstract: Cyclosporine A (CsA) is an immunosuppressive drug commonly used in organ transplant patients to prevent allograft rejections. Ketamine is a pediatric anesthetic that noncompetitively inhibits the calcium-permeable N-methyl-d-aspartic acid (NMDA) receptors.

Adverse drug-drug interaction effects between ketamine and CsA have been reported in mammals and humans. However, the mechanism of such drug-drug interaction is unclear. We have previously reported adverse effects of combination drugs, such as verapamil/ketamine and shown the mechanism through intervention by other drugs in zebrafish embryos. Here, we show that ketamine and CsA in combination produce developmental toxicity in zebrafish larvae when exposure began at 24 hours post-fertilization (hpf), whereas CsA alone did not cause any toxicity. We also demonstrate that acetyl l-carnitine (ALCAR) completely reversed the adverse effects. Both ketamine and CsA are CYP3A4 substrates. Although ketamine and CsA independently altered the expression of the hepatic marker *CYP3A65*, a zebrafish ortholog of human *CYP3A4*, both drugs together induced further increase in *CYP3A65* expression. In the presence of ALCAR however, *CYP3A65* expression was normalized. In conclusion, CsA exacerbated ketamine toxicity and ALCAR reversed the effects.

Disclosures: J. Kanungo: None. **M. Dumas:** None. **S.F. Ali:** None. **M.G. Paule:** None. **Q. Gu:** None. **B. Robinson:** None.

Poster

035. Neurodevelopmental Disorders: Transmitter Systems

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 035.11/C49

Topic: A.07. Developmental Disorders

Support: Maine INBRE

Colby College

Title: Neuroprotection by periadolescent choline supplementation in a rat model of fetal alcohol spectrum disorder

Authors: *S. STEIMEL, J. R. MITCHELL, M. TEDOLDI, A. D'AIELLO, M. GLENN
Colby Col., Waterville, ME

Abstract: Fetal Alcohol Spectrum Disorder (FASD) occurs on a spectrum and can have debilitating effects for those affected, including issues with cognition, motor development, language, and mental health. Current treatments for FASD help with some of the symptoms, but deficiencies often persist throughout an individual's lifetime. Animal models of FASD point to a potentially potent role for the essential amine, choline, to mitigate adverse outcomes; recent human studies support these findings. Choline is a dietary nutrient integral to a host of biological functions, including neuronal signaling as the precursor to acetylcholine and epigenetic modifications as a methyl donor. Choline supplementation appears to exert widespread neuroprotective effects that persist over the lifespan. Studies of FASD in rats show that postnatal

choline supplementation rescues a number of symptoms. It is possible that choline supplementation during the periadolescent period could induce restorative effects on the hippocampus by amplifying its neuroplastic functions. We previously found that both prenatal and postnatal choline supplementation increased hippocampal neurogenesis in adult rats. Additionally, hippocampal neurogenesis is reduced by alcohol in adult rats. Thus, we hypothesized that exposure to alcohol in utero would reduce adult hippocampal neurogenesis and that periadolescent choline supplementation would restore it to control levels; we tested these hypotheses in female and male rats. To do this, pregnant Sprague Dawley rats consumed a liquid diet with or without ethanol until they gave birth. The pups were cross-fostered and reared in mixed litters of female, male, control, and ethanol-treated pups until weaning on postnatal day 24. A subset of rats from each group were sacrificed at this time to examine hippocampal neurogenesis prior to the choline manipulation. The remaining rats were further divided into groups receiving either a standard choline diet or a choline-supplemented diet from postnatal day 25 to 50, then were sacrificed to assess hippocampal neurogenesis. Results presently indicate that this FASD model in rats reduces adult hippocampal neurogenesis and that periadolescent choline supplementation restores it to normal levels. We continue to study the sexually dimorphic nature of these effects and have evidence that they may be particularly robust in females. Overall, these findings offer a compelling neural substrate for findings of others of hippocampal-dependent deficits in similar rat models FASD. The present findings further bolster the therapeutic potential of choline as a dietary intervention.

Disclosures: S. Steimel: None. **J.R. Mitchell:** None. **M. Tedoldi:** None. **A. D'Aiello:** None. **M. Glenn:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.01/C50

Topic: A.10. Development and Evolution

Support: National Natural Science Foundation of China(81171152)

Title: The molecular mapping and the pioneer axon scaffold in the early developing human forebrain from 6 to 9 postconceptional weeks

Authors: *J. QIN, M. WANG, Y. QU, L. ZHOU
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Abstract: Establishment of thalamocortical reciprocal connections requires projecting axons to course several intermediate targets such as diencephalon-telencephalon junction (DTJ) and pallial-subpallial boundary (PSPB), which processes happen during early development, for

examples, embryonic days (E) 12.5-15.5 in mouse and around postconceptional weeks (WPC) 6-9 in humans. Our previous mouse studies have shown that two contingents of Isl1-pistive cells in the ventral telencephalon and prethalamus form the axonal scaffold, which extends reciprocal pioneer projections across the DTJ and guides later-reaching thalamocortical axons through the DTJ. The function of Isl1-positive cells is Celsr3 or Fzd3 highly dependent. In this study, we further studied the molecular mapping of different cell markers in WPC6-9 human forebrain and the pioneer axonal scaffold in humans. Immunostaining with anti-TBR1, -TBR2, -PAX6, -ISL1, -MASH1 and -REELIN antibodies on WPC6-9 human forebrain sections, we found these cellular makers had the similar expression patterns to those in mouse embryos. On post-conceptual week 7 human forebrain, which matches the stage of E12.5 in mice, DiI tracing shows pioneer axons from the ventral telencephalon and prethalamus also cross the DTJ. High expression of CELSR3 and FZD3 mRNA are found in these cells using RNAscope studies. In conclusion, the Celsr3 and Fzd3-dependent early scaffold maybe a similar mechanism involved in human forebrain wiring.
Keywords: axonal guidance, thalamocortical axons, mouse, human, prethalamus

Disclosures: **J. Qin:** None. **M. Wang:** None. **Y. Qu:** None. **L. Zhou:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.02/C51

Topic: A.10. Development and Evolution

Support: Brain/MINDS, AMED

JSPS KAKENHI Grant Number JP16K07036

Title: Columnar and diffuse connectivity of the marmoset PFC neurons

Authors: *A. WATAKABE[1], J. WANG[1], M. TAKAJI[1], H. MIZUKAMI[3], A. WOODWARD[2], T. KAWASE[4], H. SKIBBE[4], K. NAKAE[4], Y. YAMAGUCHI[2], S. ISHII[4], T. YAMAMORI[1]
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Abstract: The column-to-column connectivity of the monkey prefrontal cortex (PFC) neurons has been known for decades. Comparison of macaque and squirrel monkeys suggested that the “unitary” columnar size is similar across species (Bugbee and Goldman-Rakic 1983), suggesting similar organizational principles across primate species. However, due to the complexity of the prefrontal connections, there is still lack of our understanding in how prefrontal connections are organized as a whole.

We have been investigating the projection patterns of various PFC areas of marmosets by injecting TET-system-based AAV tracers, followed by serial two-photon (STP) tomography imaging (SfN 2016). The strength of STP tomography imaging is its ability to obtain detailed fluorescent images while maintaining accurate 3D information. This system is well suited to analyze columnar projections, which often requires 3D reconstruction for understanding. We optimized the STP tomography conditions so that we can efficiently image the entire marmoset brain with 50 µm slicing interval.
The injections to dorsolateral PFC areas (e.g., 8aV, 8aD, 46) resulted in spread of axons to various cortical areas including ipsi- and contra-lateral PFCs, cingular, parietal and temporal areas. We observed two modes of connections for these cases. First, column-to-column connections with axons restricted to about 300 µm. By confocal imaging, we found that presynaptic boutons can be found at all lamina depths in case of such columnar connections. In addition, we observed widespread diffuse connections in layers 1 and 6. These two modes of projections were usually coupled and observed in various areas. In our condition, AAV spread to about 700-1000 µm at the injection site. Nevertheless, axonal projections consisted of multiple 300 µm columns even for the contralateral areas, which is basically a mirror image, suggesting a mosaic organization of PFC areas. Conversely, the "diffuse" projection spread wider than the spread of injection, suggesting that this pattern is not simply a reflection of topological connectivity. We suggest that combination of column-to-column mosaic connections and widespread diffuse connections involving layers 1 and 6 form the basis of functional architecture of the primate PFC.

Disclosures: **A. Watakabe:** None. **J. Wang:** None. **M. Takaji:** None. **H. Mizukami:** None. **A. Woodward:** None. **T. Kawase:** None. **H. Skibbe:** None. **K. Nakae:** None. **Y. Yamaguchi:** None. **S. Ishii:** None. **T. Yamamori:** None.

Poster

036. Brain Evolution

Location: Halls A-C

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Topic: A.10. Development and Evolution

Support: The John Templeton Foundation Award 40463

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NIH RR¬00165 (superceded by Office of Research Infrastructure Programs/OD P51OD11132)

The Leakey Foundation #38217

Title: Oxytocin and arginine-vasopressin innervation of cerebral cortex in human and chimpanzee brains

Authors: *C. ROGERS[1,4], A. P. ROSS[6,7], S. P. SAHU[4], E. SIEGEL[4], J. DOOYEMA[5,4], M. A. CREE[5,4], E. G. STOPA[8,9], J. K. RILLING[1,2,3,7,4], H. E. ALBERS[7,6], T. M. PREUSS[5,10,7,3]
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Abstract: Oxytocin (OT) and arginine-vasopressin (AVP) are involved in the regulation of complex social behaviors across a wide range of taxa. OT is associated with social recognition, pair-bonding, and maternal bonding in rodents. In humans, OT is implicated in the promotion of trust, cooperation, and in-group altruism. AVP is associated with aggressive and territorial behaviors, but also pair-bonding, paternal behavior, and mate-guarding in males. OT and AVP exert these effects via release in the central nervous system, and their effects are mediated by the distribution of receptors across brain regions. OT and AVP v1a receptors are found in regions far from the nuclei of the hypothalamus where they are produced. This raises the question of how these peptides reach their remote receptors. Optogenetic evidence from rats suggests that projections from hypothalamic OT and AVP neurons can release peptide from axon terminals into synapses. Moreover, neuroimaging evidence shows that intranasal administration of OT and/or AVP in humans can modulate neural activity in the cortex. To determine whether OT and AVP projections actually innervate the cortex in primates, we performed immunohistochemistry for fibers containing OT and AVP in humans (n=3), chimpanzees (n=3), and rhesus macaques (n=5). We found AVP fibers in various subregions of the insular cortex in humans, including frontoinsular cortex and agranular insula. Chimpanzees exhibited lower AVP innervation of the insula, limited to the agranular insula and piriform cortex. OT fibers were found in the straight gyrus of human brains and the anterior cingulate cortex in chimpanzee brains. Our results contrast with previous reports of OT and AVP immunohistochemistry in human brains, which did not report the presence of fibers in the cortex. Interestingly, nonapeptide innervation was present in regions known to contain von Economo neurons (AVP in frontoinsular cortex in humans and OT in cingulate cortex in chimpanzees), suggesting that they may play a role in modulating the activity of this class of neurons. Overall, our results help to address the issue of how OT and AVP exert effects on brain regions far from the hypothalamus, particularly in primates, and provide evidence of species differences in OT and AVP neuroanatomy.

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Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.04/C53

Topic: A.10. Development and Evolution

Support: Mathers Foundation

Title: An interhemispheric analysis of the distribution of neurons across the cerebral cortex surface of New World monkeys

Authors: *M. GABI, E. C. TURNER, J. H. KAAS
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Abstract: What are the differences and similarities between cellular distributions in the right and left hemispheres of the cerebral cortex in primates? Our group recently demonstrated a previously unknown U-shaped distribution of neuronal densities, with higher densities in the prefrontal pole, lower densities in the intermediate area, and densities increasing again toward the occipital pole in different primate species. A similar pattern was also found in the chimpanzee neocortex, and also in four species of Old World monkeys. However, all those studies were performed in a single hemisphere which brought questions about lateralization to the surface.

To address this question, we initiate a systematic comparison of the anterior-posterior distributions of neurons and other cells in the cortical sheet of both hemispheres of New World monkeys species to determine the pattern in which the cells are allocated in the different areas of the cortex. This approach will allow us to observe if one hemisphere has any particularity in its cellular distribution when compared to the other.

We separated neocortex from the underlying white matter in both hemispheres of one *Aotus trivirgatus* and manually flattened dividing it into smaller pieces for analysis. Both hemispheres were cut in the same manner and both had 50 pieces total. Each piece of tissue was weighed and processed separately using the Isotropic Fractionator to estimate the total number of neurons and other cells across the cortical surface.

Both hemispheres exhibit a heterogeneous distribution of neuronal densities, with the lowest densities found in the frontal and the highest in the primary visual (V1) area, varying about 6-fold systematically along the anterior-posterior axis, indicating that average neuronal size is largest toward the frontal areas. The g/n ratio varies as a negative power function of neuronal density, decreasing as neuronal density increases, exactly as found in previously. This suggests that the number of glial cells per neuron in each section increases with the increasing average size of neurons. Comparing both hemispheres, we found that V1 comprises 44.3 million neurons in the right hemisphere and 44.0 million neurons in the left hemisphere (around 24% of all

neurons of the cortex).
So far, our results showed a similar pattern in the cellular distribution compared to other primates in previous studies. Overall, there are no significant differences between right and left hemispheres in the neocortex of the *Aotus*. However, a more detailed analysis is necessary to reveal additional features of the pattern of neuronal distribution in other species of New World Monkeys.

Disclosures: M. Gabi: None. **E.C. Turner:** None. **J.H. Kaas:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.05/C54

Topic: A.10. Development and Evolution

Title: U-shaped distribution of the neuronal density along the anterioposterior axis of the cerebral cortex sheds a new light on cortical expansion in Mammals

Authors: *S. E. DOS SANTOS[1], F. B. DA CUNHA[2], J. PORFIRIO[2], D. J. MESSEDER[2], P. MANGER[4], W. TAVARES[3], L. PESSOA[3], M. RAGHANTI[5], C. C. SHERWOOD[6], S. HERCULANO-HOUZEL[1]
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Abstract: The number of neurons under a unit of cortical surface area varies along the cortical anterioposterior (A-P) axis in rodents, primates, marsupials and xenarthrans, with low numbers in the frontal pole and larger numbers towards the occipital pole of the cortex (Cx). Such a single gradient of increasing neuronal densities along the A-P axis of the Cx has been attributed to a later start of neurogenesis in the occipital pole and has been suggested to be a common feature of mammalian cortices. In contrast, we recently found in primate species a U-shaped distribution of neuronal densities along the A-P axis, with higher neuronal densities in both the prefrontal and occipital poles of the Cx. This double gradient of neuronal densities argues against a simple correlation between order of neurogenesis across the cortical surface and neuronal density. Here we aim to determine if such a double gradient also exists in other mammalian species through a systematic analysis of neuronal density along the A-P axis of the Cx of acallosal (marsupials) and callosal (eutherians) species. We quantify the total number of neurons and their density in the grey matter along a full A-P series of coronal sections along the Cx of 27 species belonging to 4 mammalian clades (7 marsupials, 4 artiodactyls, 8 primates and 8 carnivorans). We used the isotropic fractionator and immunocitochemistry to NeuN to estimate numbers of neurons in the

grey matter of each section. We find that neuronal densities vary as a double gradient along the Cx of 17 species studied belonging to 3 of the 4 clades. For those species, neuronal densities are significantly higher in both the anterior and the posterior regions compared to the intermediate region (Wilcoxon, $p<0.05$). The exceptions are the largest primate cortex (human) and marsupial cortex (Western grey kangaroo), artiodactyl species, and felid carnivorans, that show a single gradient of increasing neuronal densities towards the occipital pole. The existence of a shared double gradient of neuronal densities across multiple species in mammalian clades as distant as marsupials, primates and carnivorans suggests that the mechanisms accounting for the differential distribution of neurons along the cortical A-P axis are conserved during mammalian evolution.

Disclosures: S.E. Dos santos: None. **F.B. Da Cunha:** None. **J. Porfirio:** None. **D.J. Messeder:** None. **P. Manger:** None. **W. Tavares:** None. **L. Pessoa:** None. **M. Raghanti:** None. **C.C. Sherwood:** None. **S. Herculano-Houzel:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.06/C55

Topic: A.10. Development and Evolution

Support: James S. McDonnell Foundation

Title: Cortical folding determines white matter volume and white/gray matter ratio across mammalian species

Authors: *S. HERCULANO-HOUZEL[1], S. DOS SANTOS[1], D. J. ALVARENGA[2], K. NEVES[3], R. KAZU[5], S. C. NOCTOR[6], K. G. LAMBERT[7], C. SHERWOOD[8], P. R. MANGER[9], J. H. KAAS[1], B. MOTA[4]
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Abstract: The cerebral cortex of mammals consists of two compartments: gray matter, with neuronal cell bodies, neuropil and some axons that establish local horizontal connections; and white matter, subjacent to the gray matter, consisting essentially of long-distance axons. Because the white matter of the cerebral cortex contains the components that connect neurons in the cortical gray matter to each other and to subcortical sites, the relationship between the volumes

of the two cortical compartments is key for information transmission to, from and within the cerebral cortex. It has been suggested that the volume of the white matter scales universally as a function of the volume of the gray matter across mammalian species as a whole, as expected if a global principle of wiring minimization applied (Zhang and Sejnowski, PNAS 2000). However, because we have found that the relationship between cortical volume (or surface area, or cortical thickness) and number of cortical neurons is clade-specific, whereas the degree of cortical folding is determined universally across species and clades (Mota and Herculano-Houzel, Science 2015), we decided to re-examine the issue of gray/white matter scaling separately and systematically across mammalian clades. Here we show that the volume of the white matter does actually *not* scale universally with the volume of the gray matter across mammals. Instead, the ratio between volumes of gray and white matter is universally predicted by the same equation that predicts the degree of folding of the cerebral cortex, such that the volume of the gray matter (or the ratio of gray to white matter volumes) divided by the square root of cortical thickness is a universal function of total cortical volume, regardless of the number of cortical neurons. We propose that the very mechanism that generates cortical folding through the minimization of the effective free energy associated with an expanding cortex results in compactness of the white matter to a predictable degree across a wide variety of mammalian species, regardless of the number of neurons in the cerebral cortex.

Disclosures: **S. Herculano-Houzel:** None. **S. Dos Santos:** None. **D.J. Alvarenga:** None. **K. Neves:** None. **R. Kazu:** None. **S.C. Noctor:** None. **K.G. Lambert:** None. **C. Sherwood:** None. **P.R. Manger:** None. **J.H. Kaas:** None. **B. Mota:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.07/C56

Topic: A.10. Development and Evolution

Title: Layering of neocortical cell types in the crocodilian cerebral cortex

Authors: *S. D. BRISCOE, C. W. RAGSDALE
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Abstract: All extant mammals possess a six-layered neocortex in their dorsal telencephalon. Layers serve to organize intrinsic and extrinsic neocortical circuitry: primary sensory input cells are enriched in layer IV; brainstem-projecting output neurons are found in layer V; and associational intratelencephalic projection neurons, or “IT” cells, are most abundant in layers II, III, and V. In contrast to this highly conserved mammalian cortical organization, reptiles have a relatively simple three-layered cerebral cortex. The historically dominant view of the reptilian cortex is that it corresponds to neocortical layers I, V, and VI, suggesting the upper layers are a

mammalian innovation. No detailed molecular analysis has been performed to test these presumed homologies. We studied the cerebral cortex of the American alligator *Alligator mississippiensis* at late embryonic stages by performing in situ hybridization with a panel of neocortical layer- and cell type-specific markers. Gene expression and cytoarchitectonics reveal longitudinal divisions of the dorsal cortex into lateral and medial fields. The lateral field is enriched for markers for neocortical IT cells. Strikingly, the medial field contains molecularly distinct sublamina, with an upper input-like layer and a lower output-like layer. The molecular organization of the alligator dorsal cortex resembles neither the mammalian neocortex, nor the deep layer homologies often ascribed to reptiles. These differences highlight the architectural plasticity of the dorsal telencephalon evident in amniote evolution. Future studies of extant cortical anatomies should address the divergent developmental mechanisms that organize input, output, and IT cells and the relative advantages and disadvantages of each architecture.

Disclosures: S.D. Briscoe: None. **C.W. Ragsdale:** None.

Poster

036. Brain Evolution

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Topic: A.10. Development and Evolution

Support: NRF Grant TTK14051567366

Ruhr University, Biopsychology, Bochum

Title: fMRI in nile crocodiles (crocodylus niloticus) reveals conserved sensory processing patterns in the vertebrate forebrain

Authors: *B. K. BILLINGS[1], M. BEHROOZI[2], X. HELLUY[2], P. MANGER[1], O. GÜNTÜRKÜN[2], F. STRÖCKENS[2]
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Abstract: Crocodilians are crucial for understanding the evolutionary history of amniote neural systems as they are the closest extant relatives of modern birds and share the same stem amniote ancestor with mammals. Although the crocodilian brain has been investigated anatomically, functional studies are lacking. Here we employed fMRI, never previously used in poikilotherms, to investigate crocodilian forebrain properties. Juvenile *Crocodylus niloticus* were placed in a 7T MRI scanner and BOLD signal changes recorded during presentation of visual (flickering light at 2-8 Hz) and auditory (simple: chords centered around 1000 or 3000 Hz, complex: classic music) stimuli. Visual stimulation increased BOLD signal in rostral to mid-caudal portions of the

dorsolateral dorsal ventricular ridge (DVR). Presentation of simple auditory stimuli led to signal increase in two areas of the rostro-medial and caudo-central DVR, while complex stimuli activated additional regions of the caudo-medial DVR. Activation patterns during visual stimulation resembled the projection fields of diencephalic sensory fibers, similar to birds. The recruitment of additional, presumably higher, sensory areas reflects observations made in birds and mammals, in which stimulus dependent, hierarchical processing has been reported. Our results indicate that structural and functional aspects of sensory processing have been conserved during the evolution of sauropsids, and that basic principles of hierarchical processing may have been present in the common ancestor of mammals and sauropsids. Our study shows that fMRI can be applied to gain insights into the neural processing and potential cognitive abilities of poikilotherms.

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Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.09/C58

Topic: A.10. Development and Evolution

Support: NSERC

Title: Zebrin expression in the cerebellum of crocodillians

Authors: *M. R. DANNISH[1], R. M. LONG[1], C. GUTIERREZ-IBANEZ[1], T. KOHL[2], C. E. CARR[3], R. K. TISDALE[4], I. CRACIUN[1], A. N. IWANIUK[5], D. R. WYLIE[1]
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Abstract: In both birds and mammals, the cerebellum is a highly developed convoluted structure, consisting of numerous transverse lobules. The fundamental organization of the cerebellum, however, consists of sagittal zones that are orthogonal to the lobules. This is revealed in the pattern of afferent inputs to the cerebellum, the projection patterns of Purkinje cells, and Purkinje cell response properties. The expression of several molecular markers is also parasagittally organized. The most thoroughly studied of these is zebrin II (ZII). In both birds and mammals, ZII is expressed in Purkinje cells such that there are sagittal stripes of high expression (ZII+) interdigitated with stripes of little expression (ZII-). Recent evidence suggests that the ZII+ and ZII- Purkinje cells differ with respect to the mechanism of plasticity during motor learning: ZII+ cells primarily show long term potentiation, whereas ZII- cells show long

term depression. In contrast to birds and mammals, the cerebellum is a small unfoliated structure in most non-avian reptiles. ZII expression has been examined in snakes, turtles, and lizards. In snakes and turtles, all Purkinje cells in the cerebellum are ZII+, while in lizards, there are alternating ZII+/- stripes much like in mammals and birds. In the present study we examined ZII expression in two species of crocodilians: the Nile crocodile *(Crocodylus niloticus)* and the American alligator *(Alligator mississippiensis)*. The cerebellum in these species is relatively large compared with snakes, lizards and turtles, and foliated, but not to the extent seen in birds or mammals. Because crocodilians are the closest living relatives of birds, we expected heterogeneous expression of ZII in Purkinje cells and sagittal ZII+ and ZII- stripes. However, we found that all Purkinje cells were ZII+, as in snakes and turtles. Together, these data suggest that heterogeneous expression of ZII (i.e., stripes) was either present in stem reptiles and lost three times (snakes, turtles and crocodilians), or evolved independently three times in lizards, birds and mammals, in what would represent a remarkable case of convergent evolution in brain anatomy and chemistry.

Disclosures: M.R. Dannish: None. **R.M. Long:** None. **C. Gutierrez-Ibanez:** None. **T. Kohl:** None. **C.E. Carr:** None. **R.K. Tisdale:** None. **I. Craciun:** None. **A.N. Iwaniuk:** None. **D.R. Wylie:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.10/C59

Topic: B.09. Physiological Properties of Neurons

Title: Wiring heterogeneity in the cerebellar nuclei: A link to the special morphology of the primate dentate/LN

Authors: *H. MAO[1], S. HAMODEH[1], F. SULTAN[2]
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Abstract: Compared to most other mammals, the cerebellar hemispheres are considerably expanded in size in primates and even more so in apes and humans. We have recently obtained findings that shed a new light on the special neuroarchitecture of the dentate - the main output structure of the cerebellar hemispheres. Specifically, our comparison of dendritic and axonal wiring within the rat deep cerebellar nuclei (DCN) showed a higher fiber density in the phylogenetically newer parts (i.e. the dentate/LN). A further comparison, however, between the rodents and primates revealed that the primate dentate/LN neurons show a specific difference in dendritic scaling with a much lower dendritic length per neuron leading to a smaller dendritic ROI (200µm compared to an expected 700µm) and a clustered dendritic tree. In a next step we

wanted to understand the potential synaptic changes that accompanied these differences in wiring. The DCN neurons receive their majority of inputs from the GABAergic Purkinje cells with estimates of about 67% in the cat. The remaining synapses are largely excitatory glutamatergic synapses. These glutamatergic synapses are important for the unusual high firing rates of the DCN. We therefore decided to quantify these synapses by immunohistochemically labelling them using antibodies against the vesicular glutamate transporter 1 and 2 (vGluT1 and vGluT2). We obtained unbiased random systematic 3D samples from the rat DCN with laser confocal microscopy. Using different thresholding approaches we 3D reconstructed the vGlut clusters representing synaptic boutons and obtained the profiles densities and volumes. The overall synaptic density that we obtained was 5*10^6/mm^3 for vGlut1 and 5.7*10^6/mm^3 for vGlut2. Based on our previous analysis (dendritic length density of 48 m/mm^3) we obtain a density of 94 and 125 vGlut 1 and 2 per mm dendritic length, respectively. Our estimate per DCN neuron are 188 and 250, respectively. A comparison to previous estimates of GABAergic synapses (~1700 synapses per neuron) shows that the glutamatergic synapses make up about 20% of DCN synapses and is potentially in the range of the previous estimate of 33%. In summary, our results confirm that the increased dendritic wiring in the phylogenetically newer dentate/LN is associated with a higher excitatory synaptic density. These data are important to understand the special architecture of the human dentate/LN and to establish values for comparison in cerebellar diseases such as Friedreich`s ataxia which is known to preferentially affect the human dentate/LN.

Disclosures: **H. Mao:** None. **S. Hamodeh:** None. **F. Sultan:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.11/C60

Topic: A.10. Development and Evolution

Support: Croatian Science Foundation project no. 5943

INSERM

Title: Proportion and laminar distribution of calretinin neurons in the monkey prefrontal cortex

Authors: D. SEDMAK[1], J. SCAPULA[2], D. DZAJA[1], Z. PETANJEK[1], *M. ESCLAPEZ[2]
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Abstract: Previous studies in primate associative cortex have shown that calretinin neurons represent 12% of the total neuronal pool whereas in rodents their proportion does not exceed 3%.

However it is still unclear whether such high proportion of calretinin neurons is a general feature of all primate cortical areas, whether it is layer specific and whether all these calretinin neurons are GABAergic. To address these questions we performed a quantitative study of calretinin neurons within three phylogenetically and functionally different areas of the macaque monkey prefrontal cortex (Brodmann areas 24, 32 and 9). Our results showed that calretinin labelled neurons represent around 15% of the total number of neurons revealed by NeuN immunolabelling in all examined cortical areas. Calretinin neurons were mostly located (75%) in the upper cortical layers. They account for 50% of total number of the neurons in layer I; 30% in layer II and 20% in layer III. Simultaneous immunohistochemical detection of calretinin with parvalbumin, or calbindin, showed that the population of calretinin neurons does not overlap with the other two major subpopulations of GABAergic neurons. It further demonstrated that calretinin neurons are at two times more numerous than the population of parvalbumin neurons and of calbindin neurons. These three subpopulations of GABAergic neurons account for 25% of all cortical neurons in the primate prefrontal cortex. Our data indicated that the high proportion of calretinin neurons in the upper cortical layers is a general feature of the primate prefrontal cortex. It suggests that this subpopulation of GABAergic neurons is instrumental to control information processing of a more complex cortico-cortical neuronal network.

Disclosures: D. Sedmak: None. **J. Scapula:** None. **D. Dzaja:** None. **Z. Petanjek:** None. **M. Esclapez:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.12/C61

Topic: A.10. Development and Evolution

Title: A double claustrum in marsupials?

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Abstract: Years ago we had noted, but then thought no more about it, that in their superb atlas of the brain of the American opossum(Oswaldo-Cruz and Rocha-Miranda, 1968, in their list of structures recognized and depicted were a claustrum, and also a second entity that they named the paraclaustrum. This second claustral structure had all of the appearances of a second claustrum, except there was no extreme capsule intervening between the paraclaustrum and the overlying cerebral cortex.
This paraclaustrum is a real structure, well described in the opossum atlas, and also readily viewed in Nissl and Myelin stained sections through the brain of *Didelphis virginiana* (or

Didephis marsupialis in years when that name is favored by the current crop of taxonomists of the Didelphidae.
Struck once again by the prominence of the Paraclaustrum in our own stained sections of this species, we have done a search of other marsupial brains to see if any others show anything like this Paraclaustrum. In our available sample, including the Australian marsupial species *Sminthopsis macroura, Antechinus flavipes, Sarcophilus harrisii, Isoödon obesulus, Macropus eugenii, Macropus fuliginosus, and Vombatus ursinus,* every one of them shows evidence of such an "extra claustrum". This could well be due to the relative ages and migration patterns of the capsular fibers and the claustrum cytoarchitecture, and a great deal more work on the relative connections of the two claustrums will be necessary for the generation of plausible hypotheses about how this "duplication" or rather, increase in total amount of claustral tissue, would render this distinctive structure somehow distinctive in functional role in brain networks.

Disclosures: J.I. Johnson: None. **T.T. Sheridan:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.13/C62

Topic: A.10. Development and Evolution

Support: NSF IOS #1257891

Title: Cellular scaling in brain of the nine-banded armadillo (Dasypus novemcinctus)

Authors: *N. E. POLING, A. SIECZKOWSKI, E. FAGAN, J. PADBERG
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Abstract: The distribution of neurons and non-neurons in mammalian brain structures varies significantly across species. The cellular distributions of mammalian brains have been widely studied, but quantitative examination of cellular composition of xenarthran species has not yet been described. In this study, we used the isotropic fractionation technique to determine the number of neuronal and non-neuronal cells in the neocortex, pyriform cortex, and hippocampus of the nine-banded armadillo, *Dasypus novemcinctus,* the only xenarthran species in North America. The right and left sides of each structure were processed separately. Cellular nuclei were identified by staining with 4',6'-diamidino-2-phenylindole (DAPI), and all neuronal nuclei were identified by immunocytochemistry for the neuronal nuclear antigen (NeuN). Neuronal nuclei were also secondarily stained with AlexaFluor 555 or 594 for visualization. Here we present the first quantification for neuronal and non-neuronal cell counts for the armadillo brain. The armadillos used in this study had body masses ranging from 5.0-6.1 kg and brain masses ranging from 10.7-13.9 g. We observed that the armadillo brain ranges from 36-44.1 million

non-neuronal and 4 million neuronal cells in the cortex, 49-55.7 million non-neuronal and 4.8-5.6 million neuronal cells in the pyriform cortex, and 15.5-33.5 million non-neuronal and 3-5 million neuronal cells in the hippocampus. Based on these results, the cortex is 9-10% neurons, the pyriform cortex is 8-10% neurons, and the hippocampus is 14-18% neurons. The neuron densities in these structures ranged from 1.2-1.9 million neurons per gram in the cortex, 1.8-1.9 million neurons per gram in the pyriform cortex, and 4.8-6 million neurons per gram in the hippocampus. With the data from this study, we can add xenarthrans to the large number of species whose brain cellular compositions have been previously studied. Studying the cellular distribution of the armadillo brain not only provides insight into the brain structure and function of a xenarthran species, but also enhances our understanding of cellular scaling rules across different mammalian clades and the evolution of brain structures in general.

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Disclosures: **N.E. Poling:** None. **A. Sieczkowski:** None. **E. Fagan:** None. **J. Padberg:** None.

Poster

036. Brain Evolution

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Support: NSF DRRIG

The Leakey Foundation

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The COSMOS Club

Title: Ecological correlates of mammalian hippocampal subfield neuroanatomy

Authors: *B. M. SCHILDER, C. C. SHERWOOD
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Abstract: The hippocampus is essential for long-term memory storage and retrieval as well as spatial navigation across many species. However, this structure shows considerable variation in morphology and performance across species. Only in humans is the hippocampus known to serve additional memory functions such as volitional retrospection as well as prospection of future events. However it is currently unknown what evolutionary selective pressures drove the emergence of these human cognitive features. We therefore tested the relationships between hippocampus-related ecological variables and various measures of the hippocampus and its functionally distinct subdivisions across a sample of 8 non-human primate species as well as tree shrews (*Tupaia belangeri*) and mice (*Mus musculus*). Volumetric estimates of the hippocampal complex and its constituent subdivisions included: entorhinal cortex (EC), parasubiculum (PaS), presubiculum (PrS), subiculum (Sub), cornu ammons areas 1-3 (CA1, CA2, CA3), and dentate gyrus (DG). Residual volumes for each subfield (EC_res, PaS_res, PrS_res, Sub_res, CA1_res, CA2_res, CA3_res, DG_res) were calculated for each species using phylogenetic generalized least squares (PGLS) with maximum likelihood estimation. Each residual set was then used as a response variable in a series of PGLS multiple regression analyses (which excluded humans) in which all of the following ecological variables were predictors: Population Density, Group Size, Home Range Size, and Residual Home Range Size (derived from a PGLS regression of Home Range Size against Adult Body Size, since these variables are known to scale together). These ecological data were collected from the online databases PanTHERIA and All the World's Primates. The ecological model was for the variables EC_res, PaS_res, CA1_res, and CA3_res after correcting for multiple comparisons (α=0.0016). Of particular note, PaS_res showed the most number of significant ecological relationships, including Group Size (R^2=0.81, p=0.0002), Home Range (R^2=0.84, p=0.0001), and Residual Home Range Size (R^2=0.89, p<0.00001). CA1 also showed three significant relationships, with Group Size (R^2=0.77, p=0.0005), Home Range Size (R^2=0.82, p=0.0002), and Residual Home Range Size (R^2=0.84, p=0.0001). Given that past research has demonstrated that PaS is involved in memory recall and prospection, while CA1 is more closely associated with spatial navigation ability, these results suggest that these neuroanatomical regions and the cognitive capacities they subserve may have co-evolved with social system dynamics and foraging behaviors.

Disclosures: B.M. Schilder: None. **C.C. Sherwood:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.15/D1

Topic: A.10. Development and Evolution

Support: ANR PALL-E-NODY

Title: Mesencephalic origin of the preglomerular nucleus and the inferior lobe of the "hypothalamus" in zebrafish

Authors: *S. BLOCH[1], M. THOMAS[1], I. COLIN[1], P. AFFATICATI[2], K. YAMAMOTO[1]
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Abstract: Although the overall plan of construction of the brain is conserved throughout vertebrates, significant differences exist within each brain region. Current models of the brain organization are largely based on a mammalian-centric point of view, but comparative analyses including teleost brains provide new perspectives on the general organization of the vertebrate brains.
By taking advantage of tamoxifen-inducible cre/lox system in zebrafish (Galant et al., Developmental Biology 2016), we demonstrate that some teleost structures that have been considered to be prosencephalic (forebrain) are actually mesencephalic. At 24 hours post-fertilisation (hpf), the transcription factor her5 is specifically expressed in progenitors of the midbrain hindbrain boundary (MHB). We traced the progenies during the development up to the adult stage, and found that a fraction of the MHB originating cells participates in the formation of the preglomerular nucleus (PG) and the inferior lobe (IL).
PG is a major sensory relay nucleus in teleosts, similarly to the thalamus in amniotes. The PG has been thought to be located in the ventral diencephalon. Our data show that an important ventral portion of the PG originates from the MHB, suggesting that the similar functional properties found in the amniote thalamus and the teleost PG are convergent evolution. The inferior lobe (IL) is a structure that is not found in tetrapods. It develops around the caudolateral extension of the lateral recess (LR) and was assumed to be the posterior part of the hypothalamus. Our data show that the majority of the IL is actually mesencephalic.
These results support that in spite of the functional and behavioral similarities observed, there are important variations in brain structures when comparing different vertebrate groups.

Disclosures: S. Bloch: None. **M. Thomas:** None. **I. Colin:** None. **P. Affaticati:** None. **K. Yamamoto:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.16/D2

Topic: F.01. Neuroethology

Title: Bats possess the molecular and anatomical substrate for a laryngeal motor cortex

Authors: *A. NEVUE[1], P. LOVELL[1], C. MELLO[1], C. V. PORTFORS[2]
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Abstract: The ability to learn a vocal repertoire by imitation forms the basis of human spoken language acquisition. However, the neural circuitry and mechanisms underlying this vocal learning remain poorly understood. While much of our current knowledge of the brain pathways and mechanisms related to vocal learning derives from songbirds, studies are largely lacking in mammalian species due to limited evidence for the evolution of vocal learning in mammals. Here, we examined whether the brain substrates of vocal learning are present in bats, a group of mammals with complex social and echolocation vocalizations, and some behavioral evidence for vocal learning, but where vocal pathways are undescribed. Specifically, we examined whether the molecular and connectivity features that are shared by cortical vocal areas between humans and songbirds are also present in Seba's short-tailed bats (*Carollia perspicillata*), a highly gregarious species with a complex social repertoire. Using *in situ* hybridization, we discovered that several genes that are differentially expressed in the laryngeal motor cortex (LMC) in humans and in the analogous robust nucleus of the arcopallium (RA) in zebra finches are also differentially expressed in an anterior medial area in the dorsal cortex of bats. Using these gene expression patterns to define coordinates for tract tracer injections, we found that this putative vocal motor cortex sends a direct projection to brainstem motor neurons that are thought to control the larynx. Cortical projections to brainstem vocal motor neurons are considered specific to vocal learners, as similar projections have been found in humans and vocal learning birds (songbirds, parrots and hummingbirds), but are absent or only rudimentary in non-vocal learning species. Our results suggest that bats possess the molecular and anatomical substrates to control the output of learned vocalizations, analogous to vocal learning birds and humans. We propose that bats can be used as a mammalian model for vocal learning studies, allowing for a greater understanding of the genetics and circuitry involved in human communication.

Disclosures: **A. Nevue:** None. **P. Lovell:** None. **C. Mello:** None. **C.V. Portfors:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.17/D3

Topic: A.10. Development and Evolution

Title: The development of neural specializations in birds

Authors: *D. MACLEAN-BLEVINS
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Abstract: Birds occupy a wide range of habitats and each species is uniquely adapted to best exploit the resources available in their particular niche. Some birds are sensory specialists, having evolved heightened senses to, for example, locate prey or navigate over long distances. Accompany these specializations are enlargements to brain regions that process this information; a larger brain region provides more neural processing power. The relative importance of their sensory systems can therefore, be reflected in brain anatomy. This has led to a huge amount of diversity in brain morphology and structure among birds. The aim of this project is to compare brain development in an unspecialized bird (chicken, *Gallus gallus domesticus*) to those that have a specialized sensory system (mallard, *Anas platyrhynchos* and barn owl *Tyto alba*) to determine the developmental mechanism that have led to the differentiation of brain morphology and structure in birds. We compared the size of the olfactory bulb (OB), optic tectum (OT), nucleus mesencephalicus lateralis, pars dorsalis (MLd) and the principal sensory trigeminal nucleus (PrV) in age match embryos across multiple development stages. Differences between altricial (barn owls) and precocial (mallard and chickens) species was also examined to determine if these development modes affect the timing of the enlargement to particular brain regions. Results suggest that differences between species results from speeding up neural growth early on in development, rather than extended neural growth later on in development. In mallards, the relative size of PrV and the OB were adult like about midway through development. A similar feature was also seen in barn owls, although this differences arose later on in development.

Disclosures: D. Maclean-Blevins: None.

Poster

036. Brain Evolution

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Program#/Poster#: 036.18/D4

Topic: A.10. Development and Evolution

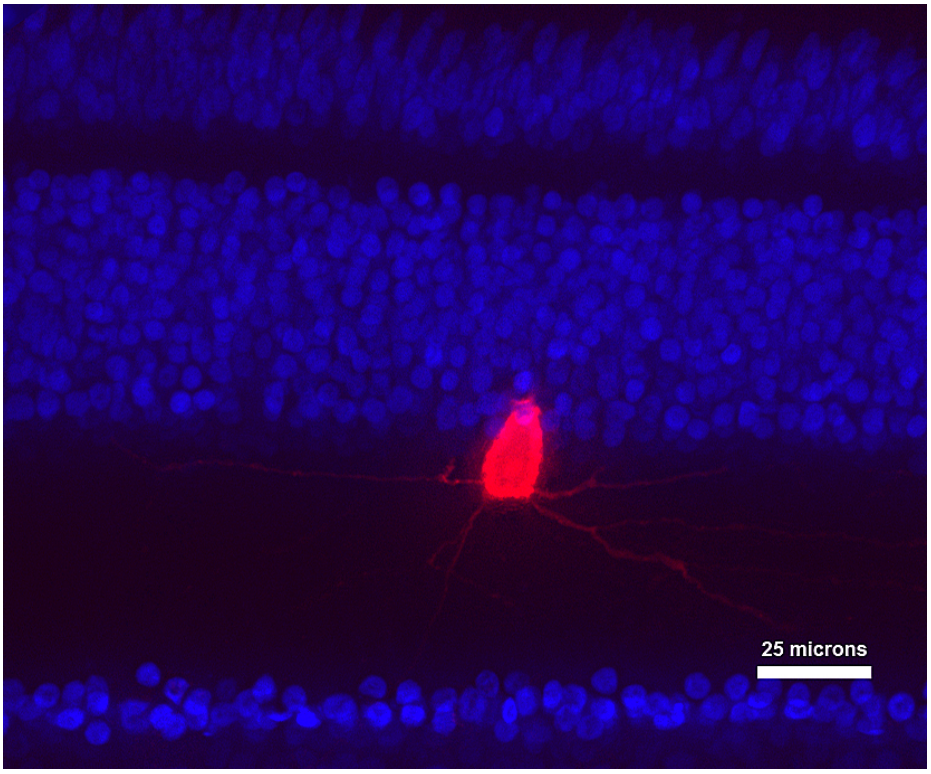
Support: NSERC (to DRW and DLA)

Title: Displaced ganglion cells project to the pretectal nucleus lentiformis mesencephali in zebra finches (taeniopygia guttata) and hummingbirds (calypte anna)

Authors: *D. R. WYLIE[1], A. H. GAEDE[2], C. GUTIERREZ-IBANEZ[1], D. L. ALTSHULER[2]
[1]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [2]Zoology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: In birds, the nucleus of the basal optic root (nBOR) and the nucleus lentiformis mesencephali (LM) are retinal recipient nuclei involved in the analysis of optic flow and the generation of the optokinetic response. It has been shown in both pigeons and chickens that the

majority of the retinal inputs to the nBOR arise from the displaced ganglion cells (DGCs), which are found at the margin of the inner nuclear and inner plexiform layers, rather than the ganglion cell layer. The LM receives afferents from retinal ganglion cells, but whether DGCs also project to LM is a matter of some debate. Bodnarenko et al. (1988) examined retinal labeling resulting from large injections of retrograde tracer in LM of chickens and concluded that DGCs did not project to LM. They found that retinal ganglion cells were retrogradely labeled from all injections, but DGCs were labeled only after injections that spread into the optic tract. Because the LM is located about 2 mm lateral to the nBOR, it is unclear how the spread of an injection into the optic tract adjacent to the LM would label fibers of the basal optic root. More recently, Wylie et al. (2014) made small injections confined to LM and found that both retinal ganglion cells and DGCs were retrogradely labelled. These findings leave open the question if there are species differences with respect to the DGC projection to LM. In the present study we made small injections of retrograde tracer (fluorescent detran, MW=3000) into the LM in a zebra finch and an Anna's hummingbird. In both cases, retrogradely labeled retinal ganglion cells and DGCs were observed. We concluded that a retinal input to the LM arising from DGCs is characteristic of most, if not all, birds.



Disclosures: D.R. Wylie: None. **A.H. Gaede:** None. **C. Gutierrez-Ibanez:** None. **D.L. Altshuler:** None.

Poster

036. Brain Evolution

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Topic: A.10. Development and Evolution

Support: Natural Sciences and Engineering Research Council of Canada (402677)

Human Fron- tier Science Foundation (RGP0003/2013)

Title: Pretectal projections to the oculomotor cerebellum in hummingbirds (C. anna), zebra finches (T. guttata), and pigeons (C. livia)

Authors: *A. H. GAEDE[1,2], C. GUTIERREZ-IBANEZ[2], M. S. ARMSTRONG[1], R. M. LONG[2], D. L. ALTSHULER[1], D. R. WYLIE[2]
[1]Zoology, Univ. of British Columbia, Vancouver, BC, Canada; [2]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada

Abstract: As birds move through their environment, large-field visual motion, or global optic flow, is processed by two retinal recipient nuclei, the nucleus of the basal optic root (nBOR) and the nucleus lentiformis mesencephali (LM). Information from these nuclei converges in the oculomotor cerebellum (folia VI-VIII) and folium IXcd of the vestibulocerebellum. The LM is further divided into lateral (LMl) and medial (LMm) subdivisions. In pigeons, it was previously reported that the projection to IXcd was largely from LMl, with fewer inputs from LMm (Pakan and Wylie 2006). Conversely, the LM projection VI-VIII arises largely from LMm, with fewer inputs from LMl. The LM is hypertrophied in hummingbirds (Iwaniuk and Wylie 2007) and differences in LM cell response properties exist between Anna's hummingbirds, zebra finches and pigeons (Gaede et al., 2017). In the present study, we aimed to determine whether there are differences in the distribution of projections from the LM to IXcd versus VI-VIII in these three species. We injected retrograde tracers (cholera toxin B-AlexaFluor 488/594) into IXcd and VI/VII in Anna's hummingbirds (n = 5), zebra finches (n = 4) and pigeons (n = 2) to identify the location of LM neurons that project to these regions. Immunohistochemical labelling for calretinin and nissl staining aided the identification of structures and borders in the pretectum. In hummingbirds and zebra finches, the projections to IXcd were largely from LMl, as seen in pigeons. However, while inputs to the oculomotor cerebellum (VI-VIII) largely arise from the LMm in pigeons, few retrograde labelled neurons were seen in LMm in hummingbirds and zebra finches from injections in VI-VII. Rather, in these species the majority of the retrograde labelled neurons in the pretectum were located medial to LMm in the nucleus laminaris precommissuralis (LPC) and nucleus principalis precommissuralis (PPC). These species differences in projection patterns may underlie different physiological demands.

Disclosures: **A.H. Gaede:** None. **C. Gutierrez-Ibanez:** None. **M.S. Armstrong:** None. **R.M. Long:** None. **D.L. Altshuler:** None. **D.R. Wylie:** None.

Poster

036. Brain Evolution

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Topic: A.10. Development and Evolution

Support: NIH/NIA AG045571

NIH T32 AG20506

NIH/NIA AG13854

The Davee Foundation

The Florane and Jerome Rosenstone Fellowship

Title: Shades of gray in human white matter

Authors: ***T. GEFEN**, G. KIM, C. GEULA, M.-M. MESULAM
Cognitive Neurol. and Alzheimer's Dis. Ctr., Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL

Abstract: In 1867, Theodor Meynert first described neurons in the white matter of the human adult brain. Interest in these oddly-placed neurons resulted in hypotheses regarding their biochemical signature, physiological function, and putative role in disease states, but were mainly derived from animal studies. In general, distribution and extent of neurochemical signatures in white matter neurons have not been comprehensively described in the human brain. Here, we investigate these cells in a series of eight whole-brain human postmortem specimens stained for distinct markers of cortical neurons. Double staining was used to evaluate co-localization of neurochemicals and to determine if the presence of one enzymatic reaction occludes another.
Two topographically distinct populations of neurons emerged. One subpopulation appeared to arise from developmental subplate neurons, and was distributed between layer VI cortical neurons and the superficial white matter. The other group reflected deep, subcortical neurons of the white matter. Both populations appeared to be neurochemically heterogeneous, showing positive reactivity to acetylcholinesterase (AChE) but not choline acetyltransferase (ChAT), neuronal nuclei (NeuN), nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d), microtubule associated protein (MAP-2), somatostatin (SOM), non-phosphorylated neurofilament protein (SMI-32), and calcium-binding proteins calbindin-D28K, calretinin, and

parvalbumin (PV). PV, in specific, was more richly expressed in superficial as opposed to the deep white matter neurons, suggesting a possible neurochemical dissociation of these two subgroups. NADPH-d, a surrogate for nitric oxide synthase, allowed for the striking morphological visualization of subcortical white matter neurons. NADPH-d-positive subcortical neurons tended to embrace the outer walls of microvessels, suggesting a functional role in vasodilation and regulation of blood flow. The presence of AChE positivity in these neurons, but not ChAT, suggests that they are cholinoceptive but non-cholinergic.
In conclusion, white matter subcortical neurons constitute two distinct subpopulations, do not display a single neurochemical identity, and their unexpected high density in deep subcortical regions implies a significant functional role. Characterization of these subcortical white matter neurons also raises critical questions regarding the vulnerability of white matter integrity in neurodegenerative illnesses.

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Poster

036. Brain Evolution

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Topic: A.10. Development and Evolution

Support: NIH/NIMHD grant #G12 MD007597

NIH/NIAAA grant AA021262

Title: A fetus with craniorachischisis and how anencephaly informs human neurodevelopment

Authors: *S. N. REID[1], F. R. WILKS, Jr.[1], R. DIOGO[1], M. C. GONDRE-LEWIS[1,2]
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Abstract: Anencephaly is a fatal neural tube defect (NTD) in which closure of the neural tube fails to occur at the rostral end of the developing fetus. The neural tube is a single cell sheet of pluripotent embryonic precursors, which, via several cascades of events result in the mature central nervous system (CNS). When neural tube formation is disrupted, a number of NTDs may arise ranging in severity from spina bifida occulta to anencephaly, frequently accompanied by spinal column abnormalities. According to the CDC, it is estimated that about 3 pregnancies in every 10,000 in the United States will have anencephaly (MMWR Morb Mort Wkly Rep., 2015). A number of factors have been attributed to the development of anencephaly: folate deficiency, chromosomal abnormalities, and defective molecular signaling. In previous studies, our lab has rigorously analyzed specimens with genetically-induced craniofacial malformations and found

that these defects inform human neural patterning (Gondré-Lewis et al., 2015; Reid et al., 2015). As was hypothesized in our previous work, examination of this anencephalic fetus will further strengthen our insight into the influence of neural tissue dynamics on CNS development. Here we provide an in-depth analysis of malformations in a cadaveric fetus with craniorachischisis, a severe form of anencephaly with spinal column involvement. Fine gross dissection was employed using watchmaker forceps to examine the cranium, cranial nerves, craniofacial skeleton, spinal column, and spinal cord. Terminology follows Grant's Atlas of Anatomy, (Agur and Dalley, 2008). A standard centimeter was included in each photograph for comparative measurement of dimensions. Radiographic imaging was used to investigate the bony properties of the fetus. Deleterious effects in the cranial and neural patterning of the fetus included, but were not limited to, significant deviation of the spinal column, absence of the superior contributions of the spinal cord, underdevelopment of both the lesser and greater wings of the sphenoid bone, and failed closure of the spinal column in the location of the cauda equinae. However, there was conservation of lumbar contributions of the spinal cord from L1 to L5 and of extraocular muscles bilaterally. Since secondary neurulation contributes to the formation of the caudal spinal cord to S2, filum terminale, and cauda equinae, we posit that the signaling of secondary neurulation influences lumbar vertebrae at the level of S2. Perhaps the preservation of secondary neurulation may offer protection from L2 onward to the termination of conus medullaris. Thus, this body of evidence may help to inform human evolutionary development of the CNS.

Disclosures: S.N. Reid: None. **F.R. Wilks:** None. **R. Diogo:** None. **M.C. Gondre-Lewis:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.22/D8

Topic: A.10. Development and Evolution

Support: NSERC

AIHS

CRC

Title: Using the isotropic fractionator method to assess the effects of domestication on neuronal and non-neuronal cell numbers in the rat (Rattus norvegicus)

Authors: *L. WILLIAMS[1], A. NGWENYA[2], R. STRYJEK[3], K. MODLINSKA[3], W. PISULA[3], S. M. PELLIS[1], A. N. IWANIUK[1]

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Abstract: Domestication is the process by which wild organisms are adapted for human use. Over time, isolated populations raised in captivity begin to diverge phenotypically from their wild counterparts in both morphology and behaviour. The lab rat, an important model organism in scientific research, is the result of domestication of the wild Norway rat *(Rattus norvegicus).* Similar to other domesticated animals, lab rats have relatively smaller brains compared to wild rats. Although the "ecological niche" of a domesticated lifestyle produces changes in brain size, little is known about the underlying neuroanatomical changes responsible for differences in brain morphology between domesticates and their wild counterparts. For example, changes in overall brain size or in the size of brain regions in domesticates could reflect changes in neuron size, connectivity or neuron number. Here, we used the recently developed isotropic fractionator technique to test for differences in the cellular composition in the brains of female wild Norway rats and two widely used laboratory strains: Long-Evans and Sprague-Dawley. The isotropic fractionator is a non-stereological means of estimating total number of cells, neurons, and non-neuronal cells in the entire brain, or any dissectible region. This technique is faster compared to traditional stereological methods and provides accurate estimate of neuron numbers, particularly for brain regions that are highly heterogeneous (e.g., neocortex) or have exceptionally high neuronal density (e.g., cerebellar granule cells). All of the rats were perfused with paraformaldehyde and the brain dissected into four main regions: olfactory bulbs, cortex, cerebellum and 'rest of brain'. After homogenization, aliquots of nuclei were incubated with DAPI and labeled immunohistochemically for neuronal nuclear antigen (NeuN). Counts of all cells (DAPI) and neurons (NeuN) were then made with a hemacytometer and the number and density of total cells and neurons calculated. The total number of cells in the cerebellum differed significantly across strains, but not for the other three brain regions. The number of neurons in the cerebellum, cortex and rest of brain also varied significantly across strains, but did not for the olfactory bulbs. Finally, the number of non-neuronal cells did not vary significantly across strains. We conclude that domesticated rat strains do differ from wild rats in the cellular composition of the brain, but that the effect of domestication varies across strains and brain regions.

Disclosures: L. Williams: None. **A. Ngwenya:** None. **R. Stryjek:** None. **K. Modlinska:** None. **W. Pisula:** None. **S.M. Pellis:** None. **A.N. Iwaniuk:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.23/D9

Topic: A.10. Development and Evolution

Support: NSERC

CRC Program

CFI

Title: A comparative analysis of retinal ganglion cell numbers and optic tectum size in birds

Authors: *A. N. IWANIUK[1], R. EL-ANDARI[1], E. FERNANDEZ-JURICIC[2], B. A. MOORE[2], T. J. LISNEY[3], C. GUTIERREZ-IBANEZ[3], D. WYLIE[3]
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Abstract: The size and anatomy of sensory regions in the brain are dependent on the amount of sensory input. Thus, more cells in sensory organs should translate to larger regions processing sensory information in the central nervous system. Although this scaling relationship between the peripheral and central components of sensory systems is generally accepted, there are relatively few empirical tests of the strength of this relationship across species. Determining to what extent the number sensory cells in the periphery are associated with the size of sensory regions in the brain is important to understanding species differences in sensory abilities and brain morphology. Here, we specifically examine the visual system in birds to test the relationship between retinal ganglion cell (RGC) numbers and the size of the optic tectum. The optic tectum receives the majority of retinal efferents in birds and we therefore predicted a strong correlation between the number of RGCs and tectum size across species. RGC counts were taken from literature or directly measured from wholemount preparations. Optic tectum size measured using unbiased stereology from the same individual specimens wherever possible. The total number of RGCs increases with brain and optic tectum sizes, but the allometric relationship is strongest with optic tectum. In contrast, peak RGC density is negatively correlated with brain and optic tectum sizes. Given these allometric relationships, we also examined the number of RGCs and optic tectum size relative to brain size. Overall, species with relatively more RGCs do have a relatively larger tectum. This is particularly true for kingfishers, which have an exceptionally high number of RGCs and relatively large optic lobes. In contrast, no significant correlation between relative RGC density and optic tectum size was detected. Although there is a general increased in relative optic tectum size with a relative increase in RGCs, the relationship varies among groups. For example, there is no correlation between relative number of RGCs and optic tectum size in owls. Owls do differ from other birds in that they have a much higher proportion of retinal efferents that project to the thalamofugal system, rather than the tectofugal system, which could explain why they are outliers to this general pattern. Waterfowl and parrots also appear to be offset from other birds such that they have relatively few RGCs compared with tectum size. Despite these variations among groups, we conclude that the size of the tectum is indeed related to the number of RGCs and suggest that similar relationships occur in other sensory systems.

Disclosures: **A.N. Iwaniuk:** None. **R. El-Andari:** None. **E. Fernandez-Juricic:** None. **B.A. Moore:** None. **T.J. Lisney:** None. **C. Gutierrez-Ibanez:** None. **D. Wylie:** None.

Poster

036. Brain Evolution

Location: Halls A-C

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Program#/Poster#: 036.24/D10

Topic: A.10. Development and Evolution

Support: NSERC

CFI

Title: Quantifying hippocampal neuronal morphology in a seasonally reproducing rodent, Richardson's ground squirrel

Authors: *B. E. BRINKMAN[1], A. NQWENYA[2], B. E. KOLB[1], A. N. IWANIUK[1]
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Abstract: Many seasonally reproducing mammals undergo significant changes in size of the brain and individual brain regions throughout the year. These seasonal changes can then interact with sex differences allowing large sex differences in the spring to become less pronounced or completely absent in the fall. To date, most research on sex-season interactions on brain morphology in mammals has largely focused on volumetric measurements. In songbirds, seasonal changes in sizes of some brain regions are the product of increases in neuron size and dendritic branching, but the extent to which similar changes occur in mammals and the interaction between sex and season on neuronal morphology are not well understood. Here, we examine seasonal and sex differences in neuronal morphology in a wild, seasonally reproducing rodent, Richardson's ground squirrel (*Urocitellus richardsonii*). This species has significant sex and seasonal differences in behaviour, making it ideal for examining sex-season interactions on brain anatomy. Female Richardson's ground squirrels live in kin-based social groups whereas male social behaviors are limited to reproduction or agonistic interactions during the breeding season. In the non-breeding season, males are almost asocial and spend time collecting and caching food for hibernation whereas females remain social and do not cache food. Previous research has shown that there are marked sex-season interactions on hippocampal neurogenesis and the size of the hippocampus, entorhinal cortex and medial prefrontal cortex. For this initial study, we tested the extent to which the morphology of hippocampal pyramidal neurons varied with sex and season. Wild Richardson's ground squirrels were trapped in the field and the brains placed in Golgi fixative. The processed tissue was then scanned under high magnification (40x or 100x) in z-stacks with a high-resolution slide scanner to create virtual slides. Neuronal morphology and measured dendritic spine density were then analyzed in these virtual slides using Neurolucida 360. The resulting measurements (e.g., soma size, dendritic complexity, dendritic length, volume) were separated into CA1 and CA3 and analyzed with two-way

analyses of variance. Although preliminary, our results represent the first attempt to examine the interaction of sex and season on neuronal morphology in a wild mammal.

Disclosures: B.E. Brinkman: None. **A. Nqwenya:** None. **B.E. Kolb:** None. **A.N. Iwaniuk:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.25/D11

Topic: A.10. Development and Evolution

Title: Comparative anatomy of extraocular muscles and orbital neurovascular structures in cetaceans and other marine mammals

Authors: *K. MESHIDA[1], S. LIN[2], P. WANG[2], E. H. GILLAND[1]
[1]Anat., [2]Radiology, Howard Univ. Col. of Med., Washington, DC

Abstract: This study examines eye muscles and orbital neurovascular structures of marine mammals to distinguish oculomotor characters shared with phylogenetic outgroups from ones uniquely adapted to aquatic life. Orbits of nine cetacean species (Smithsonian National Museum of Natural History, NMNH), one sirenian (Florida Fish and Wildlife Commission) and one carnivoran (NMNH) have been dissected macro- and microscopically. Three have been scanned by MRI in the Radiology Department at Howard University Hospital. Muscle samples were sectioned and stained by H&E and Trichrome for histological analysis. Four recti, two obliques, a multi-slip retractor bulbi and a substantial smooth orbitalis layer are present in all species. Each rectus has two bellies: palpebral and scleral. The scleral insertions, typical for all vertebrates, are very small and tendinous while the palpebral insertions are fleshy and well-developed in all species. Adjacent recti fuse near their palpebral insertions to lesser or greater degrees. Mild fusion was seen in both toothed and baleen whales of a variety of sizes and in *Trichacus manatus*; extensive fusion of the recti was seen only in middle-sized toothed whales (*Tursiops truncatus*, *Stenella coerureoalba*, *Grampus griseus*). Superior and inferior obliques penetrate the superior and inferior recti, respectively, and insert into the sclera in all cetacea. The insertions of superior obliques are broad and tendinous in most species but are more muscular in *Grampus*, *Stenella* and *Kogia*. Based on the weakly developed scleral bellies of rectus muscles, the obliques appear mainly responsible for eye movements in most cetacea. The robust medial rectus scleral belly in *Stenella* and *Grampus* indicates more function in convergence for binocular frontal vision. Three circular muscle layers have been identified. The first encircles the external surface of the EOMs and is found in all the cetacean species. In the fin whale *Balaenoptera physalus* a second layer adheres to the scleral surface of the EOMs and a third layer crosses the ventral side of the inferior rectus. The circular muscle histology is typical for smooth muscle. In

baleen whales, numerous arteries penetrate the muscles and reach the ophthalmic *rete mirabil*e which surrounds the optic nerve. Additional bundles of elongated arteries are located between the retractor bulbi and recti. The conical shape of the circular muscles suggest that they squeeze the extraocular muscles and globe, thus protruding the eyeball in antagonism to the retractor bulbi. The well-developed palpebral insertions of the recti appear to be synergists to the retractor bulbi, pulling the adnexa inward during ocular retraction.

Disclosures: K. Meshida: None. **S. Lin:** None. **P. Wang:** None. **E.H. Gilland:** None.

Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.26/D12

Topic: A.10. Development and Evolution

Support: JSPS KAKENHI Grant Number 16J03625

Title: Ascending visual pathways and activation of visual centers by light stimulation in teleosts

Authors: H. HAGIO, M. SATOU, H. ABE, *N. YAMAMOTO
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Abstract: Two ascending visual pathways to the telencephalon have been found in mammals. One of the pathways is called the geniculate system, in which retinal input is relayed to the striate cortex by the lateral geniculate nucleus in the diencephalon. The other is called the extrageniculate system, in which visual information reaches the extrastriate cortex via the superior colliculus in the mesencephalon and the lateral posterior nucleus-pulvinar complex in the diencephalon. Similarly, two pathways have been also found in birds, reptiles, amphibians and cartilaginous fishes. In actinopterygians, cypriniform fishes (such as the goldfish, *Carassius auratus* and the asian carp, *Cyprinus carpio*) possess two visual systems, while only an extrageniculate system was identified in holocentriform fishes (such as the squirrelfish, *Holocentrus ascensionis*). Thus, more detailed comparative morphological studies are necessary to understand the evolution of visual pathways in actinopterygians. We investigated the visual pathways of a gobiiform fish, the yellowfin goby, *Acanthogobius flavimanus* (Gobiiform is a taxon that emerged later than holocentriform). We found by tract-tracing methods with biotinylated dextran amine or biocytin that a visual pathway terminates in the lateral, dorsal, and central parts of the dorsal telencephalic area through the optic tectum and the nucleus prethalamicus (PTh). This pathway may be equivalent to the extrageniculate system. So far, a visual pathway similar to the geniculate system has not been observed. We studied the activities of cytochrome c oxidase (COX) by enzyme histochemistry in yellowfin goby or medaka, *Oryzias latipes* to investigate central structures activated by light stimulation. 17-50 days after the right

eye enucleation, the experimental fish were stimulated by repetitive ON-OFF of the illuminated light (0.5 Hz) for 5 minutes. COX staining in the dorsal telencephalon and PTh was denser than those in the control fish bilaterally. COX staining in the contralateral optic tectum was lower than those of enucleated side. Overall, the results suggest activation of enzyme activities by light stimulation in central structures constituting the extrageniculate system. Distribution of visual pathways in currently accepted phylogenetic tree suggests that common ancestors of actinopterygians probabaly possessed two visual systems. However, in more recently diverged species belonging to acanthopterygians, such as the squirrelfish, the goby fish and medaka, the geniculate system might be lost for some reason. Studies in other actinopterygians are required for better understanding of the evolution of teleost visual pathways.

Disclosures: H. Hagio: None. **M. Satou:** None. **H. Abe:** None. **N. Yamamoto:** None.

Poster

036. Brain Evolution

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Program#/Poster#: 036.27/D13

Topic: A.10. Development and Evolution

Support: Creighton University Center for Undergraduate Research and Scholarship Fund

Title: Comparison of behavioral tests to assess fear and anxiety in a teleost, Danio rerio, and an amphibian, Xenopus tropicalis

Authors: B. HASSMAN[1], E. DORCHUCK[1], C. M. PRINCE[2], K. REIDELBERGER[2], K. L. KRAMER[2], *L. L. BRUCE[2]
[1]Biol., [2]Biomed. Sci., Creighton Univ., Omaha, NE

Abstract: The zebrafish (*Danio rerio*) and tropical clawed frog (*Xenopus tropicalis*) have emerged as models for studying the evolution of the nervous system. Behavioral paradigms have been established for evaluating *Danio*, but comparable paradigms are not available for *Xenopus*. Three behavioral tasks were compared in *Xenopus* and *Danio* as a basis for future studies of the evolutionary roles of various genes in regulating fear behaviors. In tests measuring chronic anxiety, *Xenopus* tadpoles spent a similar amount of time in both halves of the well whether a moving stimulus was present or not. However, they spent significantly more time near the edge than the center when a moving stimulus was present versus absent. In contrast, *Danio* spent similar lengths of time near the edge whether or not the moving ball was present, but they spent significantly more time in the half of the well without movement. Second, an avoidance conditioning assay tested combined hippocampal and amygdalar learning. *Xenopus* tadpoles have a blue preference and typically swim from a red to blue compartment within 25 s. Tadpoles that received a shock upon entering the blue compartment had a significantly greater average

time prior to entering the blue compartment the following day, whereas those with no shock treatment were not significantly different in the first and second days. *Danio* have a dark preference and showed a similar light/dark response before and after shock treatment. Third, a cued fear conditioning assay tested amygdalar memory**,** using freezing as an index of fear. *Xenopus* and *Danio* rarely froze during the 50 s after exposure to 8 s of red light (adaptation trials). During learning trials the last second of red light was paired with a shock, and they responded with increased average freezing ratios. During extinction trials *Xenopus* approached normal freezing levels after 10 trials, whereas *Danio* reached normal freezing levels after 5 trials. The chronic anxiety test showed that young *Xenopus* respond to stressful conditions by increasing their edge preference, whereas *Danio* respond by moving away from the stimulus. The avoidance conditioning revealed that, although both species prefer a blue/black compartment to red/white, they remain in the red/white compartment longer than control animals after a shock was received in the blue/black compartment. The cued fear conditioning assay showed that both species learn to associate a red light with a shock and extinguish this behavior when the red light was presented without a shock. Overall, our results showed that *Xenopus* tadpoles and *Danio* exhibit responses similar to those reported in rodents, thus proving to be valuable models in the study of fear and anxiety.

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Poster

036. Brain Evolution

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 036.28/D14

Topic: A.10. Development and Evolution

Title: On the origin of nervous systems: The versatile gut hypothesis

Authors: *J. W. GRAHAM
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Abstract: Functional movement is the essence of life and nervous systems evolved to generate it efficiently in multicellular animals. However, the evolutionary relationship among the multiple vertebrate nervous systems is poorly understood. In addition to the central nervous system (CNS) are the peripheral (PNS), enteric (ENS), and autonomic (ANS) nervous systems.
All living species generate internal movements to create appropriate living conditions for the cells of their bodies. Most animals, unlike plants, must also generate external movements in order to acquire food and other necessities of life. If an animal doesn't eat, it doesn't continue to live. The question arises: do animals move to eat, or eat to move?
The gut is a versatile organ, giving rise not only to all the specializations of the digestive tract,

but also branching to produce the lungs, liver, pancreas, gallbladder, and more. The ENS, embedded within the gut tube, is often called “the second brain” as it has as many neurons as the spinal cord and operates autonomously. Here I propose the “versatile gut” hypothesis (VGH): that the gut is the archetypal tube, the ENS is evolutionarily the first brain, and the gut/ENS tube is the ultimate progenitor of all the nervous systems.
The vertebrate body plan has been described as a “tube within a tube”: the internal tube being the gut (ENS) and the external tube being the body (PNS). Most of the rest of the body also consists of innervated tubes: the respiratory, cardiovascular, urogenital, and lymph systems are all tubes, and even the CNS is a tube. Where do all the tubes and their nervous systems come from?
VGH argues that animals are largely composed of cuticle-producing, skin-covered, waterproof, innervated muscular (CSWIM) tubes. VGH argues that the first bilaterally symmetric animal was a single wormlike CSWIM tube. Wrapping the tube around itself like an elongated torus produced an animal consisting of a tube within a tube, with an internal body cavity in between, where new organs developed.
It is well-established that the vertebrate CNS tube is an invagination of the outer body tube, and according to VGH, a second generation copy of the ENS. The neural crest of vertebrate embryology gives rise to the ANS and has been called a “fourth germ layer”. VGH proposes that the neural crest is evolutionarily another invagination of the body tube into itself, forming an internal atrium surrounding the internal organs that was originally continuous with the outside world. VGH can parsimoniously explain the origin of the multiple nervous systems as copies of the ENS. This poster will present anatomical, phylogenetic, and genetic evidence in support of VGH.

Disclosures: J.W. Graham: None.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.01/D15

Topic: B.02. Ligand-Gated Ion Channels

Title: Proximal residues of the first transmembrane domain of α4 and β2 nicotinic acetylcholine subunits help express extracellular domain receptors

Authors: *G. B. WELLS, A. M. PERSON
Mol. & Cell. Med., Texas A&M Univ. Hlth. Sci. Ctr., College Station, TX

Abstract: Background: Extracellular domain (ECD) receptors from α7, α4, α3, β2, and β3 nicotinic receptor subunits that are truncated after the first transmembrane domain (M1) have functional and structural similarity to full length nicotinic acetylcholine receptors (nAChRs). Their smaller size and reduced transmembrane sequence might have advantages for structural

studies and for understanding structural and functional roles of extracellular and transmembrane domains in Cys-loop receptors. The conserved Cys-loop of the ECD interacts with proximal residues of M1 in crystallographic structures of full-length receptors. This interaction might be important for subunit designs that include an ECD-terminal protease site that liberates water-soluble ECD α4β2 nAChRs.
Objective: Determine whether extending the ECD with residues from proximal M1 followed by a native M1 affects expression of ECD α4β2 nAChRs. This design might host a protease site upstream from the native M1 while concurrently providing a native-like environment for interactions between the ECD and proximal M1.
Methods: Human α4 and β2 cDNAs were truncated after M1 (α4M1 and β2M1). Six or nine residues from the proximal end of M1 were added to the end of the ECD by mutagenesis, producing an extended ECD followed by the native M1. For comparison, sequences unrelated to M1 were added to the end of the ECD. Subunits were expressed in *Xenopus laevis* oocytes. Immunoblotting and yield of immunoisolated [^{3}H]epibatidine binding sites assessed expression of subunits and ECD α4β2 nAChRs.
Results: Extending the ECD with six M1 residues maintained expression of ECD α4β2 nAChRs. Extending the ECD with nine M1 residues decreased expression by about 50%. Increased length or residue-specific properties of the extension are possible causes for lower expression. Mixing ECD-extended α4M1 or β2M1 subunits with β2M1 or α4M1 subunits modestly affected expression. Extending the ECD with sequences unrelated to M1 had modest to severe adverse effects on expression. A point mutation in proximal M1 of α4M1 or β2M1 severely affected expression, demonstrating the importance of proximal M1 residues to ECD α4β2 nAChRs.
Conclusions: Interaction between the Cys-loop and proximal M1 residues might be important for ECD α4β2 nAChRs that are designed to functionally unlink the two domains for investigations of domain-specific functional properties. Extending the ECD with residues from M1 shows promise as a foundation for designing subunits with protease sites for *in vitro* preparation of water-soluble ECD α4β2 nAChRs. How length and residue-specific properties in extensions of ECDs affect ECD α4β2 nAChR expression needs more investigation.

Disclosures: G.B. Wells: A. Employment/Salary (full or part-time):; Texas A&M University.
A.M. Person: A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant DA040047

NIH Grant DA036061

NIH Grant DA037161

Title: α4α6β2* and not α4β2* or α6β2* nAChRs are upregulated by nicotine concentrations sufficient for evoking conditioned place preference

Authors: *B. J. HENDERSON[1], A. T. AKERS[1], Z. J. BAUMGARD[1], S. MCKINNEY[2], H. A. LESTER[2]
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Abstract: Tobacco addiction is considered the most prolific cause of preventable death in America as it contributes ~440,000 premature deaths annually. Nicotine, the primary addictive component in tobacco, is rewarding and reinforcing because it activates dopamine (DA) neurons in the ventral tegmental area (VTA) by binding to nicotinic acetylcholine receptors (nAChRs). The activation of nAChRs on these VTA DA neurons results in the release of DA in the nucleus accumbens as well as the prefrontal cortex and hippocampus. Given the low concentration of nicotine that is present in a smoker's brain (100 to 500 nM), only high sensitivity nAChRs are activated by smoking-relevant concentrations of nicotine: α4β2*, α6β2*, and α4α6β2* nAChRs. In this study, we investigated how α4α6β2* nAChRs on VTA DA neurons are altered by nicotine concentrations sufficient to evoke reward-related behavior in mice using a conditioned place preference (CPP) assay (0.5 mg/kg, intraperitoneal injection). For this, we employed mice that contain α4-mcherry and α6-GFP nAChR subunits. Using confocal microscopy and pixel-based FRET methods, we identified regions on VTA DA neurons where α4-mCherry and α6-GFP nAChR subunits co-assembled to form α4α6β2* nAChRs. We observed no significant upregulation of α4(non-α6)β2* or α6(non-α4)β2* nAChRs following a nicotine dosing paradigm that is consistent with CPP assays. However, we observed a significant upregulation in α4α6β2* nAChRs. Using pixel-based FRET (NFRET) methods we examined the changes in α4α6β2* nAChR stoichiometry. Compared to control (saline-treated) α4-mCherryα6-GFP mice, nicotine treatment caused an increase in NFRET pixels but a decrease in mean NFRET intensity. This suggests that nicotine may stabilize the $\alpha4\alpha6(\beta2)_3$ nAChR stoichiometry. Together, these data highlight the importance of nAChRs that contain both the α4 and α6 nAChR subunit and suggest that α4α6β2* nAChRs on VTA DA neurons play a significant role in the cellular changes that mediate the addiction to nicotine. Support: Marshall University Research Corporation and National Institutes of Health: DA040047 (BJH), DA036061 (HAL), DA037161 (HAL), and DA037743 (DA037743).

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Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

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Program#/Poster#: 037.03/D17

Topic: B.02. Ligand-Gated Ion Channels

Support: DA035430

NS090903

Title: Direct measurement of "trapping" of weak base nAChR ligands in a4b2 receptor-containing acidic vesicles

Authors: *A. P. GOVIND[1], Y. VALLEJO[2], J. R. STOLZ[3], J.-Z. YAN[3], G. T. SWANSON[3], W. N. GREEN[1,4]
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Abstract: The nicotinic acetylcholine receptor (nAChR) ligand, varenicline (Chantix), is thought to promote smoking cessation as a partial agonist competing with nicotine for rapid nAChR activation on mesolimbic dopaminergic neurons. Previously we presented evidence of an alternative mechanisms by which varenicline acts. Varenicline and another weak base nAChR ligand, lobeline, prevented nicotine upregulation of α4β2-type nicotinic receptors (α4β2Rs) in live cells, but not for membrane preparations. Effects on upregulation depended on intracellular pH homeostasis and were not observed if acidic pH in intracellular compartments was neutralized. The results indicated that varenicline and lobeline were trapped when protonated as weak bases in acidic compartments, and slowly released, blocking ^{125}I-epibatidine binding and desensitizing α4β2Rs. Nicotine and dihydro-beta-erythroidine, other weak base nAChR ligands with lower pK_as and α4β2R affinities were not significantly trapped. Here we show that epibatidine, with similar pK_a and α4β2R affinity, is trapped like varenicline and lobeline. Using ^{125}I-epibatidine, we have directly measured epibatidine trapping and slow release from acidic vesicles, which is easily distinguished from of ^{125}I-epibatidine unbinding from α4β2Rs due to ~100-fold slower kinetics. No trapping of ^{125}I-epibatidine occurred in cells lacking α4β2Rs, thereby demonstrating that the presence of α4β2Rs is required for trapping to occur. α4β2Rs in small acidic vesicles were imaged using α4 subunits tagged with pH-sensitive pHluorin. The numbers of α4β2R-containing acidic vesicles and α4β2R levels in the vesicles increased in parallel to increases in ^{125}I-epibatidine trapping and binding. Our findings demonstrate that smoking cessation reagents alter nicotine-induced upregulation through a novel mechanism in which weak base trapping is enhanced by α4β2Rs in acidic vesicles and by a nicotine-induced redistribution of α4β2Rs to acidic vesicles.

Disclosures: **A.P. Govind:** None. **Y. Vallejo:** None. **J.R. Stolz:** None. **J. Yan:** None. **G.T. Swanson:** None. **W.N. Green:** None.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.04/D18

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH R21 NS082902

Barrow Neurological Foundation

Title: Nicotinic acetylcholine receptor α9, α10 and β4 subunits are coordinately regulated in mouse immune cells and can co-assemble to form functional receptors

Authors: *V. A. ENGLE[1], L. M. LUCERO[1], A. KARAGIARIDI[2], R. J. LUKAS[1], P. WHITEAKER[1]
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Abstract: Multiple immune cell types have been shown to express nicotinic acetylcholine receptor (nAChR) α9 and α10 subunits. First identified in cochlear hair cells, these ancient members of the cys-loop ligand-gated ion channel family display an unusual pharmacology whereby nicotine is an antagonist. Further, both α9 and α10 subunits appear able to contribute to functionally-relevant agonist binding interfaces when expressed in *Xenopus* oocytes. In the immune system, and specifically under the inflammatory conditions observed in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis, our prior work shows that knocking out or antagonizing α9*-nAChR with nicotine results in a significant delay in disease onset, coupled with reduced disease severity.
We first surveyed the panoply of nAChR subunit genes expressed across multiple mouse immune cell types, purified via FACS, using qPCR. Testing was performed under control and inflammatory disease conditions. Multiple cell types exhibit enhanced α9 and α10 subunit mRNA levels in EAE mice at peak disease. nAChR β2 subunits are the most abundantly expressed β subunits, but their levels are not influenced by disease state. The β3 subunit is the rarest and most sporadically expressed. Intriguingly, nAChR β4, α9 and α10 subunit mRNAs are coordinately up-regulated during disease in several cell types. To determine whether these subunits can co-assemble to form functional nAChR, we conducted two-electrode voltage clamp recording in oocytes expressing different human subunit compositions, including an L9'S gain-of-function β4 subunit mutant as a functional marker. Despite previous studies not finding α9*-nAChR assemblies with wild-type β subunits, we find augmented function of agonist-activated nAChR responses in oocytes expressing β4[L9'S] subunits along with α9 alone or α9+α10

subunits. Surprisingly, when the β4[L9'S] construct is expressed alone, oocytes exhibit large leak currents that are sensitive to mecamylamine blockade but are not responsive to nicotinic agonists. This implies that β4[L9'S] subunits are trafficked to the cell surface and form spontaneously-opening ion channels, but not functionally-relevant agonist binding sites. nAChR assemblies of α9 and α10 subunits along with unconventional partners such as β4 subunits extend nAChR diversity and – in particular – may contribute to inflammatory events. Interestingly, in a preliminary screen of human immune cell populations, α9, α10 and β4 subunits are coexpressed in all but anti-inflammatory T_{reg} cells and M2 macrophages.
Supported by NIH R21 NS082902 (RJL), and the Barrow Neurological Foundation (PW & RJL).

Disclosures: V.A. Engle: None. **L.M. Lucero:** None. **A. Karagiaridi:** None. **R.J. Lukas:** None. **P. Whiteaker:** None.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.05/D19

Topic: B.02. Ligand-Gated Ion Channels

Title: The quest for selective modulators of α5-containing nicotinic acetylcholine receptors

Authors: *P. HEUSLER[1], J.-C. MARTEL[1], A. NEMECZ[4], P. SCHAMBEL[2], G. FAURE-KUZMINSKA[4], R. SIMÓ-VICENS[4], D. CUSSAC[3], P.-J. CORRINGER[4], P. SOKOLOFF[3]
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Abstract: Genomic and epidemiologic data have demonstrated a link between polymorphisms on the α5 nicotinic acetylcholine receptor (nAChR) subunit and smoking, in particular for the non-silent α5 single-nucleotide polymorphism rs16969968, inducing a partial loss of function phenotype. These observations make the α5 nAChR subunit a potentially interesting pharmacological target. However, specific pharmacological tools for α5-containing nAChRs are lacking. We therefore undertook a research program to develop tools that may allow the identification of α5-specific modulators. While the α5 subunit is described as an auxiliary subunit, not contributing to the nAChR agonist binding sites, a promising strategy is an evaluation of the interface of α5 with other subunits, in analogy to results obtained with several nAChRs subtypes. In particular, we hypothesized that the α5-α4 interface on $(\alpha4\beta2)_2\alpha5$ nicotinic receptors may contain a modulatory site. In order to develop pharmacological tools to study this hypothesis, we molecularly engineered α4 and α5 subunit superimposed sequences on acetylcholine binding proteins (AChBP) in order to mimick an α5-α4 interface on a monopentameric mutated AChBP, as previously described for α7-α7 interfaces. The mutated apo-AChBP was crystalized and structural information was used for molecular modeling,

allowing prediction of possible positive compounds that were then tested by surface plasmon resonance (SPR), allowing identification of binders with differential affinities vs wild type AChBP. However, positive binders so far could not be shown to specifically interact with $(\alpha4\beta2)_2\alpha5$ nAChRs receptors in a X. oocytes electrophysiological functional assay. In a parallel approach, the mutated AChBP was used to generate VHHs (nanobodies) specifically targeting the α5-α4 interface. High-affinity binding to the α5-α4 AChBP was confirmed by SPR for two nanobodies, and competition against small-molecule binders was demonstrated for one of these. Both nanobodies did not, however, selectively modulate α5-containing α4β2* nAChRs. These preliminary data suggest that the α5-α4 interface has a specific pharmacology, which may be amenable to development of selective compounds interacting with this interface.

Disclosures: **P. Heusler:** A. Employment/Salary (full or part-time):; Pierre Fabre Research Institute. **J. Martel:** A. Employment/Salary (full or part-time):; Pierre Fabre Research Institute. **A. Nemecz:** None. **P. Schambel:** A. Employment/Salary (full or part-time):; Pierre Fabre Research Institute. **G. Faure-Kuzminska:** None. **R. Simó-Vicens:** None. **D. Cussac:** A. Employment/Salary (full or part-time):; Pierre Fabre Research Institute. **P. Corringer:** 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.; Pierre Fabre Research Institute. **P. Sokoloff:** A. Employment/Salary (full or part-time):; Pierre Fabre Research Institute.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.06/D20

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH

Agencia Nacional de Promoción Científica y Tecnológica

Title: Unraveling the evolutionary history of nicotinic acetylcholine receptor subunits

Authors: *I. MARCOVICH[1], M. LIPOVSEK[2], A. TRIGILA[1], L. FRANCHINI[1], P. PLAZAS[1,3], A. ELGOYHEN[1,3]
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Abstract: The pentameric ligand-gated ion channels superfamily comprises a number of receptors which includes the nicotinic acetylcholine receptors (nAChRs). These are expressed in

the central and peripheral nervous system, the neuromuscular end-plate and the auditory epithelium. Neuronal nAChRs can assemble from a variety of subunits: α2- α8 and β2- β4; whereas the inner ear hair cells nAChRs only assemble from α9 and α10 subunits. The α9α10 nAChR exhibits peculiar characteristics that distinguish it from the rest of the nAChRs. For instance, in contrast to all nAChRs that serve excitatory neurotransmission, the activation of α9α10 nAChRs produces hyperpolarization of the postsynaptic cell, since it is coupled to small conductance calcium-dependent potassium channels. Previous work has determined that mammalian α10, but not other nAChRs subunits, has been under positive darwinian selection and acquired several non-synonymous substitutions in the coding region (Franchini and Elgoyhen, 2006). This is accompanied by differences in calcium permeability of α9α10 receptors across vertebrate species (Lipovsek, et al. 2012). Given that α9α10 is the only nAChR expressed in inner ear hair cells, we propose that these acquired amino acid changes in the primary sequence of the α10 subunit are the basis for functional diversity across species in the case of α9α10. On the contrary, neuronal nAChRs can achieve differential channel properties by assembling from the wide variety of subunits expressed in the brain. Therefore, we hypothesize that 1- the biophysical properties of the α9α10 nAChRs should vary across different vertebrate species, but those of neuronal nAChRs should be conserved and 2- the expression pattern of neuronal nAChRs should vary across vertebrate species. We conducted a comparative analysis of the biophysical properties of recombinant rat (mammalian), chicken (avian) and frog (amphibian) α9α10, α7 and α4β2 receptors expressed in *Xenopus laevis* oocytes. α9α10 nAChRs from the three species present striking differences in their desensitization rate, calcium permeability and modulation and current-voltage curves. In contrast, in the case of neuronal receptors these properties are conserved when comparing rat, chicken and frog receptors. These results suggest that the differential functional properties of the α9α10 nAChRs across species resulted from the peculiar evolutionary process to which mammalian α10 was subjected. In the case of neuronal nAChRs subunits, the acquisition of differential channel properties might be achieved by differences in subunit combinatorial assemblies across species.

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Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.07/D21

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH grant R01 GM103801

NIH grant P01 GM48677

Barrow Neurological Foundation Funds

Title: Functional isoforms of α9α10 nicotinic acetylcholine receptors (nAChR) suggested by transmembrane domain 2 (TM2) mutant subunits

Authors: *L. AZAM[1], L. M. LUCERO[3], A. KARAGIARIDI[3,4], V. A. ENGLE[3], R. J. LUKAS[3], J. M. MCINTOSH[1,2,5], P. WHITEAKER[3]
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Abstract: Several nAChR subtypes have been shown to express as two functional isoforms, with α and β subunits in $(\alpha)_2(\beta)_3$ or $(\alpha)_3(\beta)_2$ ratios, often having significantly different pharmacology and/or biophysical properties. We sought to determine whether more than one α9α10 stoichiometry can also produce functional nAChRs.
Human (h) α9 and α10 nAChR subunits were generated with a V13'A mutation in the TM2 domain. It was expected that incorporation of these mutant subunits would produce a typical "gain-of-function" (GOF) phenotype, shown previously for the hα6 nAChR subunit, such as increased agonist potency and whole-cell macroscopic current. Function was tested by two-electrode voltage-clamp electrophysiology, following injection of mRNAs into *Xenopus laevis* oocytes, using wild-type (WT) human α9 or α10 subunits as positive controls. Expression of either WT hα9 or hα10 subunits alone produced little-to-no ACh-stimulated function, while co-expression of both together produced robust ACh-induced currents. Introduction of either the α9V13'A or α10V13'A together with its WT partner (1:1 ratio) resulted in a modest but significant increase in agonist potency, as measured using ACh concentration-response curves. These effects were further explored by varying the ratios of WT to V13'A subunits. For α9V13'A or α10V13'A, effects on ACh potency were subunit-ratio dependent. Interestingly, the subunit injection ratios producing optimal α9α10-nAChR function varied across $\alpha9^{wt}\alpha10^{wt}$ (9:1), α9V13'A:$\alpha10^{wt}$ (9:2), and $\alpha9^{wt}$α10V13'A (9:0.5). Further, incorporation of α9V13'A at intermediate subunit ratios produced distinctly biphasic ACh concentration-response curves, suggesting that more than one α9α10-nAChR stoichiometry may result in assembly of a functional nAChR population. Finally, incorporation of either "GOF" mutant subunit resulted in decreased function. Since the mechanisms of increased agonist potency and function-per-receptor are considered to be intimately linked, this suggests that the V13'A mutation suppresses cell-surface expression of α9α10. Significantly greater loss of function seen in the case of the α9V13'A subunit indicates that V13'A mutation effects on function differ between α9 and α10 subunits.
Since the hα9 and hα10 V13'A mutations did not yield the expected GOF seen for the hα6V13'A mutation, it is possible that optimal GOF location(s) may lie elsewhere in the TM2 region of the α9 & α10 subunits. Additional subunit substitutions in this area will be made to determine that. Residues V5' and L9' will be specifically focused on, as mutation of the corresponding residues in the muscle α subunit has previously been shown to enhance ACh potency.

Disclosures: L. Azam: None. **L.M. Lucero:** None. **A. Karagiaridi:** None. **V.A. Engle:** None. **R.J. Lukas:** None. **J.M. McIntosh:** None. **P. Whiteaker:** None.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.08/D22

Topic: B.02. Ligand-Gated Ion Channels

Support: NINDS 1R15NS090368-01

Title: Molecular dissection of oxantel specificity for the alpha4beta2 nicotinic acetylcholine receptor

Authors: *M. M. LEVANDOSKI[1,2], L. A. CHECHIK[1], M. LOZA[1], M. KOLANOWSKI[1], A. KARAGIARIDI[1], S. S. TARDREW[1], B. FROLUND[2]
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Abstract: Allosteric modulation of neuronal nicotinic acetylcholine receptors (nAChRs) continues to be an important area of investigation for what these mechanisms can reveal about the basic function of the receptors and for potential therapeutic developments. We have focused on the anthelmintics morantel (Mor) and oxantel (Oxa) as model compounds for their allosteric modulatory activities on the α3β2 and α4β2 nAChR subtypes. These compounds both have nearly opposite effects on the two subtypes, potentiating ACh-evoked currents for α3β2 and inhibiting responses for α4β2 receptors. We have exploited these differences in order to study the specificity of interactions of the modulators with their binding sites at β(+)/α(–) interfaces. Our current work focuses on both sides of the specificity "coin," namely, probing effects of α4(–) mutants and of oxantel analogues on modulatory activity. We express nAChRs heterologously in *Xenopus* oocytes and examine their pharmacology via two-electrode voltage-clamp recordings. We find that mutating α4(–) positions homologous to α3(–) locations already known to contribute to specificity impacts modulation. For example, instead of making the receptor more α3-like in its modulation, α4H107Lβ2 appears to be more strongly inhibited than wild type α4β2. We are currently exploring the context dependence of these effects. Similarly, our initial work on Oxa analogues suggests the importance of the tertiary amine, central double bond and the *meta* hydroxyl group on the benzyl substituent, because changing these moieties alters modulation. Studying complete series of binding site mutations and modulator analogues (and combinations thereof) should pinpoint atomic-level interactions for this allosteric modulator system.

Disclosures: M.M. Levandoski: None. **L.A. Chechik:** None. **M. Loza:** None. **M. Kolanowski:** None. **A. Karagiaridi:** None. **S.S. Tardrew:** None. **B. Frolund:** None.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.09/D23

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant NS031744

Title: Single channel behavior of (α4β2)2α4 Nicotinic Acetylcholine Receptor potentiated by the allosteric modulator NS-9283

Authors: *S. MAZZAFERRO[1], I. BERMUDEZ[2], S. SINE[1]
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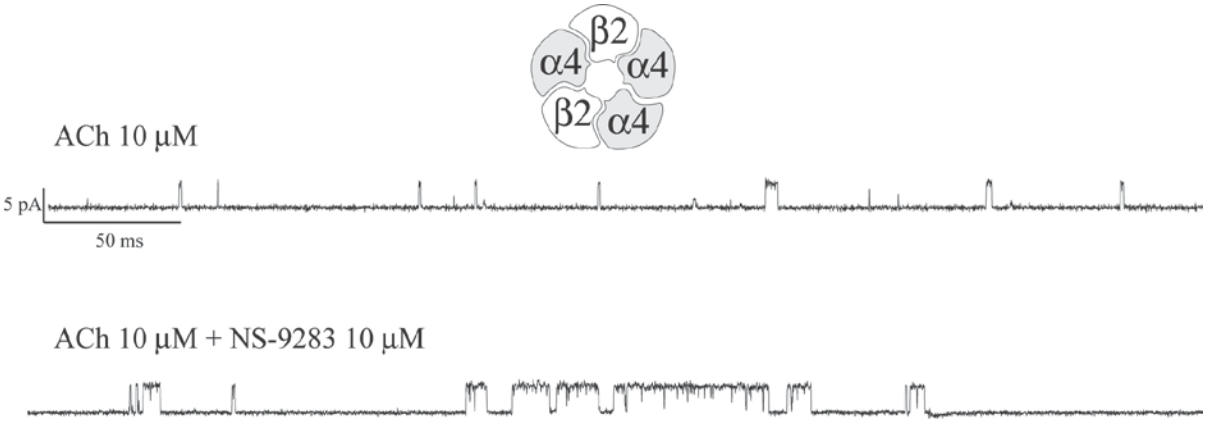
Abstract: The α4β2 nicotinic acetylcholine receptor (nAChR) is the most abundant nAChR type in the brain where it contributes to multiple brain functions and is implicated in a range of neurological diseases. α4β2 nAChRs can assemble in two stoichiometries, one with three β2 and two α4 subunits ($(\alpha4\beta2)_2\beta2$)) and the other with two β2 and three α4 subunits ($(\alpha4\beta2)_2\alpha4$)). Each stoichiometry contains two binding sites for ACh at the α4/β2 interfaces, while the $(\alpha4\beta2)_2\alpha4$ stoichiometry contains a third binding site at the α4/α4 interface. The two stoichiometries exhibit distinct neuroanatomical distributions in the nervous system. Alteration of these distributions has been observed in nicotine addiction. Design of stoichiometry-specific allosteric modulators could offer a strategy to treat nicotine addiction and minimize adverse effects. The positive allosteric modulator NS-9283 is selective for the $(\alpha4\beta2)_2\alpha4$ stoichiometry. Administration of NS-9283 attenuates nicotine self-administration and seeking in rats. Macroscopic current measurements suggest that the binding site for NS-9283 is located at the α/α4 interface. Thus potentiation could arise through a co-agonist mechanism in which the two α4/β2 sites are occupied by ACh and the α4/α4 site is occupied by NS-9283. To gain deeper insight into the mechanism of NS-9283 potentiation, we recorded single channel currents from cells expressing receptors assembled from either free α4 and β2 subunits or concatenated subunits that constrain the stoichiometry to $(\alpha4\beta2)_2\alpha4$. We find that in the presence of ACh alone, channel openings appear as random isolated events, whereas in the presence of both ACh and NS-9283, channel openings appear in clearly defined clusters of several events in quick succession. Furthermore, we identify extracellular residues, structurally distant from the α4/α4 interface, that are essential for potentiation by NS-9283. Current studies aim to discriminate binding from transduction elements involved in NS-9283 potentiation.



Disclosures: **S. Mazzaferro:** None. **I. Bermudez:** None. **S. Sine:** None.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.10/D24

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant GM58448

Title: Identifying drugs that bind to intrasubunit binding sites in the transmembrane domain of an $\alpha_2\beta\gamma\delta$ nicotinic acetylcholine receptor

Authors: Z. YU, *J. B. COHEN
Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Photoaffinity labeling studies have identified binding sites in the *Torpedo* nicotinic acetylcholine receptor (nAChR) for positive and negative allosteric modulators (PAMs/NAMs) in the transmembrane domain at the γ-α subunit interface and within the δ subunit helix bundle for inhibitors including propofol. The photoreactive anesthetic barbiturate *R*-*m*TFD-MPAB (*R*-1-methyl-5-allyl-5-(*m*-trifluoromethyl-diazirinylphenyl) barbituric acid), a nAChR inhibitor, binds to sites in the ion channel and at the γ^+-α^- subunit interface. *R*-*m*TFD-MPAB acts as a PAM of α1β3γ2 γ-aminobutyric acid type A receptor ($GABA_AR$), binding to homologous sites at the γ^+-β^- and α^+-β^- subunit interfaces. In contrast, *S*-*m*TFD-MPPB (*S*-1-methyl-5-propyly-5-(*m*-trifluoromethyl-diazirinylphenyl) barbituric acid) behaves as a convulsant and α1β3γ2 $GABA_AR$ inhibitor by binding to the same γ^+-β^- intersubunit binding site selectively in the closed channel state (Jayakar *et al.*, J. Biol. Chem. 290: 23432-23446 (2015)). In this study by use of radioligand binding assays and photoaffinity labeling, we show that *S*-*m*TFD-MPPB binds in the *Torpedo* nAChR similarly to *R*-*m*TFD-MPAB in the ion channel (Hamouda *et al.*, Mol. Pharmacol. 85:

735-746 (2014)). However, *S-m*TFD-MPPB binds to intrasubunit binding sites within the α and δ subunits but not to the γ^+-α^- intersubunit site. Based upon the inhibition of binding of the channel blockers [^{3}H]TCP and [^{3}H]tetracaine, *S-m*TFD-MPPB binds in the ion channel with >100-fold higher affinity in the nAChR desensitized state (IC_{50} = 7 μM) than in the closed channel state, and PCP inhibits [^{3}H]*S-m*TFD-MPPB photolabeling of residues at the cytoplasmic end of the ion channel. Additionally, [^{3}H]*S-m*TFD-MPPB photolabels amino acids at the lipid-protein interface (αCys412, γCys451 and γTrp453) at similar efficiency in the absence or presence of agonist. In the nAChR desensitized state, propofol inhibits [^{3}H]*S-m*TFD-MPPB photolabeling of residues contributing to the intrasubunit sites in the δ subunit (δPhe232, δThr274 and δIle288) and α subunit (αVal218). These results establish that photolabeling with [^{3}H]*S-m*TFD-MPPB can be used to monitor binding of drugs to the α subunit intrasubunit binding site and provide the first demonstration that propofol binds to that site as well as to the intrasubunit site in the δ intrasubunit and to a site in the ion channel.

Disclosures: Z. Yu: None. **J.B. Cohen:** None.

Poster

037. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 037.11/D25

Topic: B.02. Ligand-Gated Ion Channels

Title: Intracellular domains of α7 nicotinic acetylcholine receptor regulation by G proteins

Authors: *E. BAK[1], J. R. KING[1], N. KABBANI[2]
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Abstract: α7 nicotinic acetylcholine receptors (nAChRs) are amongst the most abundant type of nAChRs in the mammalian CNS and represent an important pharmacological target in the treatment of various neurodisease. How these channel receptors operate however remains unclear. In previous work we have characterized a novel G protein binding cluster (GPBC) within the human α7 nAChR intracellular loop. This receptor region was found responsible for driving G protein signaling by the ligand activated α7 nAChR in neural and immune cells. Here we show a role for additional intracellular motifs in G protein/nAChR associations. Using site directed mutagenesis we demonstrate the functional significance of two distinct GPBCs within the α7 nAChR intracellular loop and show a role for Gβγ binding in the regulation of receptor trafficking. The results suggest that intracellular interactions between the α7 nAChR and select G protein subunits are essential for the trafficking and membrane targeting of the α7 nAChR in neural cells.

Disclosures: E. Bak: None. **J.R. King:** None. **N. Kabbani:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.01/D26

Topic: B.03. G-Protein Coupled Receptors

Support: R01MH084894

R01MH111940

Title: Maternal influenza viral infection induces schizophrenia-related abnormalities that are modulated by the host microbiome in the adult offspring

Authors: *J. M. SAUNDERS[1], J. L. MORENO[1], D. KANG[2], K. HIDESHIMA[1], A. GARCIA-SASTRE[5], P. GILLEVET[6], J. BAJAJ[3], J. GONZALEZ-MAESO[4]
[1]Physiol. and Biophysics, [2]Microbiology and Immunol., [3]Dept. of Intrnl. Med., [4]Dept. of Physiol. and Biophysics, Virginia Commonwealth Univ. Hlth. Syst., Richmond, VA; [5]Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]George Mason Univ., Fairfax, VA

Abstract: It has long been known that maternal immune activation during pregnancy increases the risk of schizophrenia development in the adult offspring. Murine maternal immune activation models, such as influenza virus infection during pregnancy, produce alterations in adult offspring that reflect schizophrenia-like changes such as increased $5HT_{2A}$ receptor density in the prefrontal cortex, a finding also observed in postmortem samples from human schizophrenia patients, and increased head twitch response, a $5HT_{2A}$-dependent murine model of psychosis, in response to the human hallucinogen DOI. Schizophrenia is believed to be a disease whose development involves multiple insults, with early predispositions to the disorder resulting from factors such as maternal infection or genetic predisposition being further exacerbated by later life factors such as social stress or drug use. Evidence from preclinical and clinical work continues to show that commensal bacteria affect brain development and function. Despite these implications in other conditions and the numerous ways in which gut flora could potentially communicate with the central nervous system and serve as a second insult within schizophrenia, the gut microbiome remains largely unexplored in this condition. Here we report that, in a murine maternal immune activation model of schizophrenia involving infection of day E9.5 pregnant CD-1 mice with 5 x 10^3 pfu of the mouse adapted influenza A/WSN/33 (H1N1) virus, maternal immune activation results in alterations of the gut microbiome as determined by 16s rRNA sequencing of cecum contents and analysis by linear discriminant analysis effect size (LEfSe) relative to mock infection controls. In addition, intraperitoneal streptomycin (20 mg/kg) administered at six weeks affects components of the gut microbiome that seem to be predictive of schizophrenia-related phenotypes. These findings suggest that there are gut microbiome alterations associated with

maternal influenza virus infection during pregnancy as a preclinical model of schizophrenia, and that these alterations can be reduced by adolescent antibiotic administration.

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Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.02/D27

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01MH084894

NIH Grant R01MH111940

Title: Epigenetic role of HDAC2 in the limited therapeutic effect of the mGlu2/3 receptor agonist pomaglumetad after chronic atypical antipsychotic treatment

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Abstract: Increasing evidence suggests that glutamatergic tone is involved in the core symptoms of schizophrenia, and agonists for the metabotropic glutamate receptor 2 (mGluR2), such as pomaglumetad, have been suggested as a novel treatment for schizophrenia. Despite the inability of pomaglumetad to meet the primary endpoints in Phase II clinical trials, a recent post-hoc analysis revealed that schizophrenia patients previously treated with typical antipsychotics were responsive to pomaglumetad whereas those treated with atypical antipsychotics were not. We previously showed how chronic atypical antypsychotics treatment, such as clozapine, lead to an epigenetic-driven down-regulation of *mGlu2R.* Atypical antipsychotics also induced histone deacetylase 2 (HDAC2) up-regulation in a mechanism that involves the down-regulation of the serotonin receptor 2A (5-HT2AR) in prefrontal cortex. HDACs removal of acetyl groups from lysine residues in the N-terminal tails of core histones shifts the balance toward chromatin condensation and silences gene expression. We show that chronic-clozapine induced epigenetic changes suppress, not only the expression of mGluR2, but also of genes associated with synaptic structural remodeling and behavioral plasticity. Using chromatin immunoprecipitation (ChIP) assays we show that after chronic clozapine treatment acetylation of histone H3 (H3ac), which correlates with transcriptional activation of these genes, is strongly decreased, whereas binding of HDAC2 was significantly increased. In contrast, these repressive histone modifications induced at the promoter region of the mGluR2 gene *(Grm2)* and genes involved in synaptic

formation and plasticity were absent in the frontal cortex of HDAC2 conditional KO mice treated chronically with clozapine. Additionally, our results demonstrate that decreased H3ac binding at the promoter region of these genes is absent in the frontal cortex of 5HT2AR knock-out (KO) mice chronically treated with clozapine. Together, these findings suggest that forebrain HDAC2 function is necessary for the decreased histone acetylation at *Grm2* promoter, and its dependency on the primary target of atypical antipsychotics, the 5HT2AR. Therefore, we hypothesize that the HDAC2-dependent epigenetic-driven down-regulation of mGlu2R transcription might be responsible for the poor outcome of pomaglumetad in a sample of patients in which prior treatment with atypical antipsychotics was over-represented.

Disclosures: M. De La Fuente Revenga: None. **D. Ibi:** None. **J. González-Maeso:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

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Program#/Poster#: 038.03/D28

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01MH084894

NIH Grant R01MH111940

Title: Trafficking pathway and mechanism through which 5-HT2A affects subcellular localization of mGlu2 in schizophrenia models

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Abstract: Class A serotonin 5-HT_{2A} receptor (5HT2A) and class C metabotropic glutamate 2 and 3 receptors (mGlu2/3) are G protein-coupled receptors (GPCRs) that have been linked to the pathophysiology of schizophrenia and other psychotic disorders, as well as to the mechanism of action of atypical antipsychotic drugs (e.g., clozapine, olanzapine and risperidone), and the new class of potential antipsychotic drugs acting as mGlu2/3 agonists (e.g., LY379268 and LY404039). Increasing evidences attest that GPCRs can form homomeric and heteromeric structural units that affect both intracellular receptor trafficking and receptor signaling. Previous findings suggest that 5HT2A and mGlu2 maintain close molecular proximity in heterologous systems and in mouse and human frontal cortex. Using an experimental system based on confocal microscopy and Imaging Flow Cytometry (IFC), here we assessed in HEK293 cells the specific components of the intracellular trafficking pathway followed by mGlu2 alone, and complexed with the 5HT2A. We show bimolecular complementation signal (BiFC) between

5HT2A-mCitrine-N172 and 5HT2A-mCitrine-C67, mGlu2-mCitrine-N172 and mGlu2-mCitrine-C67, mGlu3-mCitrine-N172 and mGlu3-mCitrine-C67, and 5HT2A-mCitrine-N172 and mGlu2-mCitrine-C67. This however did not occur in cells expressing 5HT2A-mCitrine-N172 and mGlu3-mCitrine-C67, supporting specificity of BiFC signaling. Our findings suggest that 5HT2A alone is partially retained intracellularly, co-localizing with markers of the endoplasmic reticulum (ER) and Golgi apparatus. Co-localization analyses also indicate that the 5HT2A-mGlu2 heteromer is detected in both compartments, suggesting an early assembling during the maturation pathway. Additionally, our data suggest that co-expression of mGlu2 with 5HT2A affects the pattern of co-localization of 5HT2A with ER markers. To characterize further the pattern of co-localization of 5HT2A and mGlu2 with markers of the different components of maturation and endocytic pathways, we created double stable Flp-In T-Rex HEK293 cell lines expressing inducible 5HT2A along with constitutive mGlu2 and mGlu3 receptors. Our current data suggest that 5HT2A affects sub-cellular localization of mGlu2 through a mechanism that requires heteromeric receptor complex formation, and that Rab proteins regulate intracellular trafficking of the 5HT2A-mGlu2 heteromer. Thus, components of this intracellular trafficking pathway may represent a new molecular target for schizophrenia treatment.

Disclosures: **R. Toneatti:** None. **J. González-Maeso:** None. **J.F. Lopez-Gimenez:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.04/D29

Topic: B.03. G-Protein Coupled Receptors

Support: NIH grant R15NS078645

NIH grant R15DA038092

Institutional Mentoring Environment Grant

Title: The orphan G protein-coupled receptor, GPR18 is expressed in hippocampal pyramidal cells

Authors: *J. G. EDWARDS, J. KRANEWITTER-CALL, B. ANDERSON, T. JARMON, T. CALL, K. HURST
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Abstract: Synaptic plasticity mechanisms such as hippocampal long-term potentiation (LTP) and long-term depression appear to be essential in learning and memory. While most classical plasticity studies examined NMDA receptors, the first identified to mediate LTP, other receptors including cannabinoid receptor CB1 are also involved in various types of hippocampal plasticity.

As plasticity is so critical to memory, these additional mediators of plasticity are necessary to understand in order to provide tools necessary to potentially mitigate memory disorders such as Alzheimer's disease and dementia, which still lack effective treatments. We previously identify plasticity modification by endocannabinoid pathways that were independent of canonical CB1. Therefore, we examined a novel orphan G protein-coupled receptor, GPR18, which can be activated by the endocannabinoid anandamide along with THC and endogenous lipid N-arachidonyl-glycine. Using reverse transcription real-time PCR we identified GPR18 expression in mouse hippocampus. PCR product was isolated by gel electrophoresis to demonstrate the appropriate sized amplicon, which was cut from the gel and sequenced to validate it as GPR18. To confirm PCR data, we used immunohistochemistry to examine GPR18 protein expression and location. We note antibody labeling in cell bodies of CA1, CA3 and dentate gyrus pyramidal cells. In addition, we are examining the potential physiological role of hippocampal GPR18. Collectively, our data indicate that GPR18 is expressed in the hippocampus and we hope to determine any physiologically relevant tie it may have to endocannabinoid-like plasticity in the hippocampus.

Disclosures: J.G. Edwards: None. **J. Kranewitter-Call:** None. **B. Anderson:** None. **T. Jarmon:** None. **T. Call:** None. **K. Hurst:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.05/D30

Topic: B.03. G-Protein Coupled Receptors

Title: Simultaneous exposure to chronic mild stress and enriched diets elicit differential expressions of dopamine D4 receptor in the hippocampus and prefrontal cortex of mice model

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Abstract: Dopamine D4 receptor is a synaptic gatekeeper that stabilizes glutamatergic transmission in prefrontal cortex (PFC). When neuronal activity changes in situations such as acute or repeated stress, D4 redistributes GluA2-lacking AMPARs at synapses through the bi-directional control of CaMKII. This homeostatic action of D4 provides a potential mechanism for the unique role of D4 in many stress-related neuropsychiatric disorders. The hippocampus (HC) provided the gateway into much of what we have learned about stress and brain structural and functional plasticity, and this initial focus has expanded to other interconnected brain regions, such as the amygdala and prefrontal cortex. In this study we explored the modulatory role of enriched diets on the expression of D4 receptor in the PFC and HC of mice model of chronic mild stress. Adult mice of both sexes were used, they were divided into two broad

groups: Adult mice (equal number of male and female) and prenatal mice (consisting of females and males). Each group was further subdivided into five (5): Subgroup A were fed with carbohydrate enriched diet; Subgroup B were fed with protein enriched diet; Subgroup C were fed with high omega-3 enriched diet; Subgroup D were fed with antioxidants enriched diet; Subgroup E were fed with normal mice pellets; Each of the five subgroups were made up of Stressed and Non-stressed groups. Exposure to stress and dieting commenced on day 9 of pregnancy until the 50th postnatal day (PND 50), after which they were subjected to Barne's Maze to assess spatial memory. The animals were sacrificed and the brains harvested, processed for Immuno-cytochemical staining for Dopamine (D4) and analysis. The results showed that stressed decreased the expressions of D4 in the dentate gyrus and CA3 regions of the hippocampus while increasing the expression in the prefrontal cortex. While the enriched diets increased the expression in the dentate gyrus (DG and the prefrontal cortex (PFC) when compared to their respective controls. The expressions are relatively higher in the DG and PFC of adult stressed fed with enriched diets than in the prenatally stressed mice. We conclude that enriched diets and chronic mild stress exhibit differential expressions of D4 in the PFC and HC of the exposed mice with age dimorphism

Disclosures: **P.D. Shallie:** A. Employment/Salary (full or part-time):; Olabisi Onabanjo University, Ago-Iwoye. OgunState. Nigeria. **H.B. Akpan:** None. **O.F. Shallie:** None. **R.O. Folarin:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: B.03. G-Protein Coupled Receptors

Support: UTMB Center for Addiction Research

Rising Star Award UT System

Title: Ligand screening against novel striatum-specific human orphan GPCRs identified through genome-wide human transcriptome profiling

Authors: *S. R. RAVAL[1], M. JAIN[1], R. YANG[2], S. XI[2], J. A. ALLEN[1]
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Abstract: The striatum performs essential brain functions including movement control and reward encoding; while striatal dysfunction occurs in many diseases including Parkinson's, addiction and psychosis. Of the 350 non-sensory human G protein-coupled receptors (GPCRs),

~120 remain orphan receptors whose endogenous ligands and functions are largely unknown; however, brain orphan GPCRs are potentially valuable targets for creating future therapeutics. With the goal to identify GPCRs selectively expressed in the human striatum, here we employed a genome-wide tissue transcriptome analysis and used a high throughput screening platform to find ligands active at newly identified striatal orphan receptors. We conducted a comprehensive genome-wide survey of human tissue-selective gene expression using 1640 high-quality RNA-seq samples from the Genotype Tissue Expression project. We developed a weighted tissue-selectivity scoring method that measures the similarity and differences of gene expression in all tissues and variability across donor samples. To identify receptor function and screen the ligands, human clones of receptors were expressed in HEK293 cells and signaling was assessed using the PRESTO-Tango assay or the Glo-sensor cAMP assay. As a screening validation, the PRESTO-Tango assay was used to screen the LOPAC library against striatal oGPCRs. Human gene expression analyses identified a total of 123 protein-coding genes and 76 non-coding RNAs selectively expressed in the human striatum, included striatal-selective expression of 18 GPCRs. 11 of these receptors have known ligands including many established therapeutic or investigational drug targets (dopamine D1, D2, D3 receptors, serotonin 5-HT4 and 5-HT6 receptors). The remaining 7 human GPCRs, namely, GPR6, GPR52, GPR55, GPR88, GPR101, GPR139, GPR149, were all identified as class A orphan receptors. When expressed in HEK293 cells, GPR6, GPR52 and GPR101 profoundly increased cAMP suggesting Gs/olf coupling and high constitutive activity, while GPR88 decreased cAMP levels suggesting Gi/o coupling. Initial optimization and screening results indicated all orphan receptors were appropriately plasma membrane localized and ligands modulated varying degrees of basal activity to recruit beta-arrestins. Identification of these striatal orphan receptors selectively expressed in the human striatum suggests their possible role in modulating striatal neurotransmission and regulating the basal ganglia. Our findings also suggest that pharmacological modulation of the striatal human orphan GPCRs might serve as a potential therapy for treating striatum-related neurological diseases.

Disclosures: **S.R. Raval:** None. **M. Jain:** None. **R. Yang:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **S. Xi:** A. Employment/Salary (full or part-time):; Pfizer, Inc.. **J.A. Allen:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

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Topic: B.03. G-Protein Coupled Receptors

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Title: Functional pre-coupled complexes of adenosine A_{2A} and dopamine D_2 receptor heteromers and adenylyl-cyclase

Authors: *S. FERRE[1], G. NAVARRO[2], A. CORDOMI[3], V. CASADÓ-ANGUERA[2], E. MORENO[2], N.-S. CAI[1], A. CORTÉS[2], E. I. CANELA[2], C. DESSAUER[4], V. CASADÓ[2], C. LLUÍS[2]
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Abstract: G protein-coupled receptors (GPCRs), G proteins and adenylyl cyclase (AC) compose one of the most studied transmembrane cell signaling pathways. Still controversial is the ligand-dependent mode of interactions between these signaling molecules: random collision of freely mobile membrane molecules *versus* rearrangement of pre-coupled elements in a macromolecular complex. Also controversial is the evidence that a GPCR homodimer coupled to a single heterotrimeric G protein constitutes a common functional unit. We used synthetic peptides with the amino acid sequences from transmembrane helices (TMs) of the adenosine A_{2A} receptor ($A_{2A}R$), the dopamine D_2 receptor (D_2R) and putative TMs of adenylyl cyclase subtype (AC5) to target the oligomerization interface between receptor homodimers and heterodimers and between receptors and AC5 and to demonstrate the existence and functional significance of $A_{2A}R$-D_2R-AC5 complexes. The use of these peptides together with bimolecular fluorescence complementation assays and computer modeling allowed us to establish: i) the quaternary structure of $A_{2A}R$-D_2R heterotetramer in complex with Gi and Gs; ii) the existence of intermolecular interactions between TMs of the $A_{2A}R$-D_2R heterotetramer and putative TMs of AC5; and iii) the requirement of the heterotetramer for canonical Gs-Gi interactions that allows a Gi-coupled GPCR to counteract Gs-coupled GPCR activation of AC5. The results demonstrate that GPCR heteromers constitute an essential part of pre-coupled macromolecular complexes that include specific receptors, G proteins and effectors that integrate the final signaling output of the complex.

Disclosures: **S. Ferre:** None. **G. Navarro:** None. **A. Cordomi:** None. **V. Casadó-Anguera:** None. **E. Moreno:** None. **N. Cai:** None. **A. Cortés:** None. **E.I. Canela:** None. **C. Dessauer:** None. **V. Casadó:** None. **C. Lluís:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

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Topic: B.03. G-Protein Coupled Receptors

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Hussman Foundation

Autism BrainNet

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Title: Serotonergic 5-HT1a receptor binding density in three cortical regions in autism

Authors: *C. BRANDENBURG, K. SUBRAMANIAN, G. J. BLATT
Hussman Inst. For Autism, Baltimore, MD

Abstract: Background: The role of 5-HT1a receptors in anxiety, depression, mood and emotion are well established and are the target of many widely used partial agonists including buspirone (anxiolytic) and vilazodone (anti-depressant), the latter which also acts as a selective serotonergic reuptake inhibitor (SSRI). A previous autoradiographic study from our laboratory using a single concentration of 1 nM ^{3}H-8-Hydroxy-N,N-dipropyl-2-aminotetralin (8-OH-DPAT), a full agonist for serotonergic 5-HT-1a receptors, labeled postmortem sections from two cortical areas including the posterior cingulate cortex (PCC) and the fusiform gyrus (FG) in autism and control cases (Oblak et al., 2013). Results showed a significant decrease in the autism cases in both the PCC and FG. 5-HT1a receptors are G-protein coupled receptors that exist as both presynaptic autoreceptors, especially in the raphe nuclei, and as postsynaptic receptors in limbic regions including the anterior cingulate cortex (ACC) and PCC as well as in some neocortical areas including the FG. In autism cases, all three cortical areas were also shown to have decreased GABA-ARs and GABA-BRs in previous studies. Additionally, cytoarchitectural abnormalities were found in the ACC and PCC. Objective: Conduct saturation binding assays on postmortem autism and control cases utilizing the ligand ^{3}H-8-OH-DPAT to label 5-HT1a receptors in the ACC, PCC and FG as an indication of receptor density in superficial and deep layers in each cortical area. Methods: 20µm sections from the ACC, PCC and FG (n=14-19 autism, n=18-19 controls) were incubated with ^{3}H-8-OH-DPAT, 120 nM, 90 nM and 30nM (Perkin Elmer) before being loaded into X-ray cassettes with tritium standards and apposed to tritium-sensitive hyperfilm. Two sections per case were used to determine total binding with the tritiated ligand and one section was used for non-specific binding with a competitive displacer (5-HT-HCl 100µM). After exposure, films were developed and digitized to quantify

measurements of binding in femtomoles per milligram of tissue. Analysis was performed using a student's t-test. Results: A significant decrease in 5-HT1a binding was demonstrated in autism cases in the superficial cortical layers at 90 nM in the ACC (p=0.0462) and a trend for a decrease in the same region at 120 nM. At 30mM, there was also a decrease but not at a significant level. No differences were seen in the PCC or FG. Conclusion: The ACC, a limbic cortical area involved in social-emotional behavior, reward anticipation, impulse control and high level cognitive activities may be an especially vulnerable area in autism, exhibiting alterations in both GABA and 5-HT receptors.

Disclosures: C. Brandenburg: None. **K. Subramanian:** None. **G.J. Blatt:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

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Topic: B.03. G-Protein Coupled Receptors

Support: 5R01DA03844602

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Title: Behavioral profile of a novel serotonin 5-HT_{2C} receptor (5-HT_{2C}R) positive allosteric modulator

Authors: *J. M. MISZKIEL[1], C. T. WILD[2], C. DING[2], E. A. WOLD[2], R. G. FOX[2], S. J. STUTZ[2], N. C. ANASTASIO[2], J. ZHOU[2], K. A. CUNNINGHAM[2]
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Abstract: Background: The serotonin 5-HT_{2C} receptor (5-HT_{2C}R) has been implicated in neuropsychiatric (e.g., anxiety, depression, substance use disorders) and neuropathological conditions (e.g., schizophrenia) as well as obesity and metabolic disorders. We have designed and synthesized novel chemical entities as 5-HT_{2C}R positive allosteric modulators (PAMs) as a strategy to discover 5-HT_{2C}R-targeted neurotherapeutics. To this end, compound CYD-1-79 has been characterized as a 5-HT_{2C}R PAM in cellular studies and exhibits a favorable overall pharmacokinetic profile in rats.
Aim: The aim of the present study was to assess the effects of CYD-1-79 to alter basal (i.e., motor activity, grooming) behavior, impulsivity or cocaine-evoked behaviors (i.e.,

hyperactivity), or cue reactivity (sensitivity to cues previously associated with drug-taking) observed during abstinence from cocaine self-administration in rats.
Methods: Motor activity was quantified in low-light, open field activity monitors. Self-grooming was assessed individually in plexiglass cages. The one choice serial reaction time (1-CSRT) task was employed to assess premature responses as a measure of motor impulsivity. Cue reactivity was assessed as previously-active lever presses reinforced by cocaine-associated cues (e.g., lights, pump sound) following cocaine self-administration. A drug discrimination assay was employed to assess the ability of CYD-1-79 to substitute for, or potentiate, the stimulus effects of the selective 5-HT_{2C}R agonist WAY163909.
Results: CYD-1-79 suppressed motor activity at the highest dose tested (5 mg/kg), but did not alter grooming behaviors at any dose tested (0.25-1 mg/kg). CYD-1-79 (0.5-2 mg/kg) dose-dependently suppressed premature responses in the 1-CSRT task while 1 mg/kg suppressed cue reactivity. CYD-1-79 (1 mg/kg) evoked a maximum of 45% WAY163909-lever responding. Co-administration of CYD-1-79 plus WAY163909 (at 0.5 mg/kg, each) evoked a full substitution for WAY163909.
Conclusion: These data suggest that CYD-1-79 acts *in vivo* to augment 5-HT_{2C}R agonist-induced behaviors without intrinsic efficacy at the orthosteric site of the 5-HT_{2C}R. The observation that CYD-1-79 partially substituted for WAY163909 may not be unexpected given that the effects of endogenous 5-HT could be enhanced by a 5-HT_{2C}R PAM. Additionally, allosteric modulators of receptor signaling have proven to have higher target selectivity over orthosteric-based approaches and do not trigger long-term changes in receptor regulation. Thus, these data represent evidence of a viable strategy towards the discovery of novel 5-HT_{2C}R-targeted neurotherapeutics.

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Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

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Topic: B.03. G-Protein Coupled Receptors

Support: National Science Centre, Poland, grant 2014/15/N/NZ4/04760

FW5/PM2/16

Title: Noradrenaline modulates the membrane potential in medial prefrontal cortex pyramidal neurons via β_1-receptors

Authors: *K. E. GRZELKA, P. SZULCZYK
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Abstract: The noradrenergic system is essential in the medial prefrontal cortex (mPFC) physiology: noradrenaline (NA) acting via adrenergic receptors (α_1, α_2 and β) plays a significant role in the regulation of cognitive brain functions and affective processes. Impaired modulation of the mPFC by NA has been implicated in many neuropsychiatric diseases, e.g. posttraumatic stress disorder, attention deficit hyperactivity disorder, depression. While the presence of all adrenergic receptor subtypes has been reported in the mPFC, little is known regarding the mechanisms by which NA modulates mPFC neurons. The aim of this study was to investigate which adrenergic receptor subtype controls the resting membrane potential and holding currents in mPFC neurons. Next, we wanted to define the cellular effector(s) and signalling pathway(s) involved in the action of NA. To answer these questions, we have recorded the resting membrane potential and holding currents using patch-clamp techniques. Gramicidin perforated-patch and classical whole-cell recordings were obtained from layer V mPFC pyramidal neurons in slices isolated from young Wistar rats. All tested compounds were applied to the bath and/or to the solution in the recording pipette. NA evoked depolarization of the membrane potential and the inward holding current. Stimulation of α_1- and α_2-receptors failed to evoke similar effects. Meanwhile, the nonselective β-receptor agonist as well as the selective β_1-receptor agonist mimicked the effect of NA on holding currents. The NA-dependent inward current was considerably reduced by the selective β_1-receptor antagonist. The β_1-related inward current was greatly decreased in the presence of Cs^+ ions and ZD7288, a selective blocker of HCN (hyperpolarization-activated cyclic nucleotide–gated) channels. It was not affected by selective blockers of different signaling pathways known to be responsible for mediating the effects from G-protein-coupled receptors (e.g. adenylyl cyclase-PKA, phospholipase C-PKC, protein tyrosine kinase, glycogen synthase kinase-3, CaM kinase II). However, it was significantly diminished by gallein, a blocker of the βγ subunit-dependent transduction system. We conclude that NA modulates the membrane potential and holding currents of the mPFC pyramidal neurons via β_1-receptors. The effects occur due to HCN channel activation and are mediated in a membrane delimited fashion by a βγ subunit released from the G-protein.

Disclosures: K.E. Grzelka: None. **P. Szulczyk:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

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Topic: B.03. G-Protein Coupled Receptors

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Title: Neuropeptide release from neurohypophysial terminals is modulated by zinc activation of a GPR39 pathway

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Abstract: Many synaptic vesicles/neurosecretory granules appear to contain the essential trace metal Zinc (Zn^{2+}) and deficiencies in this cation's levels seem to play a role in a number of physiological brain disorders. We have previously shown that vasopressinergic (AVP) and oxytocinergic (OT) Neurohypophysial terminals possess Zn^{2+}, its receptor GPR39, as well as IP_3 receptors. We currently show that the GPR39 pathway is indeed activated by Zn^{2+} in both terminal types. Fluo-3 imaging indicates that intraterminal Ca^{2+} ($[Ca^{2+}]i$) increases with exogenous Zn^{2+} applications in the presence and absence of extracellular Calcium. The Gq inhibitor YM254890 (2 μM) was able to inhibit the $[Ca^{2+}]i$ signal by 60% when stimulated with 200 μM $ZnSO_4$. On the other hand, the Zinc receptor agonist, GPR39-C3 (1 μM), was able to increase the $[Ca^{2+}]i$ signal by 30%; indicating that GPR39 is present and functional in NH terminals. AVP and OT release from isolated neurohypophysial terminals of Wistar rats was examined in the presence and absence of Zn^{2+} using specific ELISAs. An exogenous concentration of 6-10 μM Zn^{2+} was necessary to initiate neuropeptide release and a maximal response was obtained at a concentration of greater than or equal to 200 μM. The EC_{50} estimate for AVP was 30.25 μM and the EC_{50} estimate for OT was 20.1 μM $ZnSO_4$. This exogenous Zn^{2+} stimulation was able to cause neuropeptide release even in minimal extracellular $[Ca^{2+}]$ conditions. It has been reported that caffeine (20 mM) is able to inhibit IP_3 receptors, and thus reduce $[Ca^{2+}]i$; its effect was to inhibit the Zn^{2+}-induced release of both types of neuropeptides. In agreement with this mechanism, 10 mM Ca-EDTA, a Zn^{2+} chelator, reduced high K^+-induced release of both AVP and OT from intact neurohypophyses. These results lead us to conclude that endogenous Zn^{2+} can activate GPR39 and modulate AVP and OT release by increasing intracellular calcium levels via IP_3 receptors in neurosecretory granules of neurohypophysial terminals.

Disclosures: S. Ortiz-Miranda: None. **C. Wu:** None. **S. Malavez-Cajigas:** None. **E. Custer:** None. **B.M. Salzberg:** None. **M.M. Francis:** None. **J.R. Lemos:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.12/D37

Topic: B.03. G-Protein Coupled Receptors

Support: NIH/NIDA DA024329

Cooper Medical School of Rowan University, Internal Grants

Title: Olanzapine prevents the cannabinoid-induced upregulation of serotonin 2A (5-HT_{2A}) and dopamine 2 (D2L) receptors: Role of G-Protein Receptor 5 (GRK5)

Authors: *G. A. CARRASCO
Dept. of Biomed. Sci., Cooper Med. Sch. of Rowan Univ., Camden, NJ

Abstract: Repeat exposure to cannabinoids has been linked to disorders associated with dysfunction of serotonin 2A (5-HT_{2A}) and Dopamine 2 (D_{2L}) receptor signaling in prefrontal cortex (PFCx) such as anxiety, depression, psychosis, etc. We recently reported that repeated exposure to cannabinoids upregulates and enhances the activity of 5-HT_{2A} and D_{2L} receptors in rat PFCx and in two neuronal cell lines, A1A1v and CLU213 cells. This cannabinoid-induced upregulation is dependent on GRK5 activity, and is associated with enhanced formation of a 5-HT_{2A}-D_{2L} receptor heterodimer. Here we studied the effect of olanzapine, an atypical antipsychotic, on the cannabinoid-induced: (1) upregulation of 5-HT_{2A} and D_{2L} receptors; and (2) formation of a 5-HT_{2A}-D_{2L} receptor heterodimer.

We initially tested the effect of repeated exposure (72 hours) of non-selective cannabinoid agonist (CP55940, 1 nM), selective CB1 receptor agonist (ACEA 15 nM), or selective CB2 receptor agonist (GP1a, 1 nM) on D_{2L} receptor expression in CLU213 cells. We found that repeat CP55940 treatment significantly ($p<0.01$) increased D_{2L} receptor protein levels (99 ± 7% increase compared to controls). Interestingly, repeated treatment with either selective CB2 agonist (GP1a) or selective CB1 agonist (ACEA) significantly increased D_{2L} receptor protein levels (35 ± 7% and 39 ± 5%, respectively). Furthermore, treatment with both GP1a and ACEA increased D_{2L} receptor protein levels 76 ± 8%. Our preliminary data suggest that CB1 and CB2 receptors use different signaling mechanisms to regulate D_{2L} expression.

We also found that selective and non-selective cannabinoid agonists significantly ($p<0.01$) enhanced the formation of a 5-HT_{2A}-D_{2L} receptor heterodimer in neuronal cells. Importantly, the cannabinoid-induced formation of the 5-HT_{2A}-D_{2L} receptor dimer was significantly inhibited in cells stably expressing GRK5 shRNA, suggesting a key role of GRK5 on the formation of this heterodimer receptor. Olanzapine inhibited the cannabinoid-enhanced formation of a 5-HT2A-D2L receptor heterodimer in neuronal cells. The effect olanzapine was associated with a significant ($p<0.01$): (1) downregulation of both 5-HT_{2A} and D_{2L} receptor mRNA; (2) decrease in membrane-associated 5-HT_{2A} and D_{2L} protein levels, and (3) and a selective downregulation of GRK5 mRNA levels.

The present studies provide insight into the signaling mechanisms involved in the cannabinoid-induced formation of 5- HT_{2A}-D_{2L} receptor heterodimers. Our studies might provide insight into mechanisms that can be targeted to prevent the potential adverse effect while deriving the therapeutic benefits of cannabinoids.

Disclosures: G.A. Carrasco: None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.13/D38

Topic: B.03. G-Protein Coupled Receptors

Support: Swiss National Science Foundation Grant # 31003A-159513

Title: Evaluation of the receptor-mediated function of lactate in neuronal activity

Authors: *H. D. ABRANTES[1], M. BRIQUET[2], S. OFFERMANNS[3], J.-Y. CHATTON[4]
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Abstract: Since the introduction of the astrocyte-neuron lactate shuttle hypothesis lactate started being recognized as an energy substrate for neurons. In this model, lactate is provided to neurons by transport from astrocytes. Besides the metabolic functions of lactate, the recent discovery of a G protein-coupled receptor (GPCR) for lactate in neurons of the central nervous system, called hydroxycarboxylic acid receptor 1 (HCA1R), has pointed to additional non-metabolic effects of lactate on neuronal network activity.The aim of this work was to characterize the intracellular pathway mediated by the activation of HCA1R in neurons, and to investigate the cooperation between HCA1R and other GPCRs for the modulation of neuronal network activity. The non-metabolized agonists of HCA1R, 3,5-DHBA and 3-Cl HBA, reversibly decreased the spontaneous spiking activity of primary cortical neurons of wild-type mice by 40%. Neither compounds affected the activity of neurons prepared from HCA1R knock-out animals. We observed that HCA1R in neurons mediates its effect through the inhibition of adenylyl cyclase, decreasing cAMP levels and PKA activity. These results together with previously published data on the G_i protein deactivator PTX ability to reverse L-lactate effect in neurons, strongly supports the notion that HCA1R in the central nervous system is mediating its effect through a G_i protein, as was previously demonstrated in adipocytes. A characteristic feature of GPCRs is their ability to cross-talk with other GPCRs. We found that HCAR1 cooperates with the adenosine A1 receptor, GABAB receptor, and α_2-adrenergic receptor for the modulation of the neuronal network activity. Our results underlines the requirement of HCA1R activation and the non-metabolic nature of the lactate effects on neuronal activity. This study supports the idea that lactate can be considered a gliotransmitter able to modulate the neuronal activity through GPCRs.

Disclosures: H.D. Abrantes: None. **M. Briquet:** None. **S. Offermanns:** None. **J. Chatton:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.14/D39

Topic: B.03. G-Protein Coupled Receptors

Support: NSERC

SHRF

CFI

Heart and Stroke

Title: Systemic administration of adenosine A1 receptor agonist induces increased microglia activation and hippocampal-dependent memory deficits: Role of microglia chemokine receptor CXCR2

Authors: *H. KIM, R. K. TENEYCKE, F. S. CAYABYAB
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Abstract: We recently demonstrated that adenosine A1 receptor (A1R) stimulation in vivo by systemic administration of the A1R-selective agonist N^6-cyclopentyladenosine (CPA) increased microglia density in rat hippocampus (unpublished). Chronic A1R stimulation also increased hippocampal neuronal damage and caused hippocampal-dependent spatial memory deficits in rats. It remains unclear whether A1R-mediated microglia activation contributes to hippocampal neurodegeneration. We hypothesized that cognitive deficits and neuronal damage after chronic A1R stimulation require increased activation of microglia. By inhibiting microglia chemokine receptor CXCR2, we aimed to reduce hippocampal neurodegeneration and deficits in hippocampal-dependent spatial memory. Male Sprague-Dawley rats were injected with CPA (5mg/kg, intraperitoneal injection) with or without prior injection of CXCR2 receptor antagonist SB225002 (2mg/kg, intraperitoneal injection). 48h following injection, animals were tested using a Y-maze testing paradigm to test hippocampal-dependent spatial memory. Post-mortem tissue analysis showed that the CPA-treated rats displayed increased hippocampal neurodegeneration and neuronal damage as shown by Fluoro-Jade B and propidium iodide staining, respectively. Although CPA did not significantly increase CXCR expression in microglia located within the CA1 region of the hippocampus, the co-administration of CPA and SB225002 reversed hippocampal-dependent spatial memory deficits. Thus, these preliminary results indicate that chronic A1R stimulation induces microglia activation, which contributes to CXCR2-mediated hippocampal neuronal damage and hippocampal-dependent memory deficits. Whether a

functional interaction between A1R and CXCR2 exists to promote neuroinflammation and hippocampal neurodegeneration is yet to be established.

Disclosures: H. Kim: None. **R.K. Teneycke:** None. **F.S. Cayabyab:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.15/D40

Topic: B.03. G-Protein Coupled Receptors

Title: Transient cannabinoid receptor expression in a developing cortical parvalbumin subcircuit

Authors: *M. D. CAIATI, T. K. HENSCH
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Abstract: Cannabinoid receptors (CB1r) are powerful neuromodulators of inhibitory transmission and activity-dependent synaptic plasticity. They are thought to reside primarily in presynaptic cholecystokinin (CCK+) GABAergic terminals in both the neocortex and hippocampus. Instead, CB1r expression and function in parvalbumin (PV+) cells remains unclear, despite the well-known cannabinoid involvement in developmental plasticity and modulation of gamma rhythms, which are driven by PV+ circuitry. Here, using *in situ* hybridization and fluorescence activated cell sorting, we first demonstrate that CB1r are transiently localized to a specific subset of PV+ interneurons, in both mouse visual and prefrontal cortex. CB1r-expressing PV+ cells exhibit low PV expression and are GAD1+ and lack CCK/SST. The expression of CB1r in PV+ cells is layer-specific, experience-dependent and developmentally regulated, reaching highest levels at the peak of sensory and prefrontal critical periods for plasticity, respectively. Remarkably, activation of CB1r with the selective agonist WIN55,212-2 leads to a prominent modulation of dendritic excitability in a subset of PV+ cells, unveiling the ability of cannabinoids to control the activity of these interneurons through a previously unappreciated cell-autonomous action. This effect is completely blocked by the CB1r antagonist AM251 and follows the same developmental regulation of CB1r expression in PV+ cells. Altogether, our data strongly indicate that a subset of cortical PV+ cells is sensitive to cannabinoids during a critical window for brain development, bearing important implications for the involvement of cannabis exposure in the pathophysiology of neurodevelopmental disorders.

Disclosures: M.D. Caiati: None. **T.K. Hensch:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.16/D41

Topic: B.03. G-Protein Coupled Receptors

Title: The histamine H_3 receptor activates the phospholipase C/Ca^{2+}/protein kinase C pathway in striatal neurons in primary culture

Authors: *N. RIVERA-RAMÍREZ[1], J.-M. ARIAS[2], U. GARCÍA-HERNÁNDEZ[1], J.-A. ARIAS-MONTAÑO[1]
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Abstract: The histamine H_3 receptor (H_3R) is abundantly expressed in the Central Nervous System where it regulates several functions pre- and post-synaptically. H_3Rs are found at high levels in the basal ganglia, particularly on the bodies and nerve terminals of striatal medium spiny GABAergic neurons. H_3Rs couple to $G\alpha_{i/o}$ proteins and trigger or modulate several intracellular pathways, primarily cAMP formation and the opening of voltage-activated Ca^{2+} channels. In heterologous expression systems H_3R activation stimulates phospholipase C (PLC) resulting in an increase in the intracellular concentration of calcium ions ($[Ca^{2+}]i$). In this work we aimed to determine whether H_3R activation stimulated the PLC/Ca^{2+}/protein kinase C (PKC) pathway in striatal neurons in primary culture.
In striatal primary cultures the H_3R agonist immepip induced a significant increase in IP_3 formation and this effect was reduced by the PLC inhibitor U-73122 (10 μM). Changes in $[Ca^{2+}]i$ were studied by microfluorometry, and in 18 out of 70 cells (25.7%) perfusion with immepip (1 μM) increased the $[Ca^{2+}]_i$. Confocal microscopy confirmed the H_3R-mediated increase in the $[Ca^{2+}]_i$ in a group of striatal neurons (18.2%), and the response was also detected in medium with no added $CaCl_2$. Confocal microscopy also showed that the activation of dopamine D_2 receptors with the agonist quinpirole (10 μM) increased the $[Ca^{2+}]_i$ in a sub-population of neuronal cells. Cells responded with an increase in the $[Ca^{2+}]_i$ to either the H_3R agonist immepip or the D_2R agonist quinpirole, but not the same cell to both agonists. PLC activation produces diacylglycerol (DAG) which alone or in combination with Ca^{2+} ions stimulates the classical and novel isoforms of PKC. We therefore evaluated whether PKC plays a role in H_3R-mediated ERK1/2 phosphorylation. The agonist immepip induced maximal phosphorylation of ERK1/2 at 5 min, and this effect was reduced by the PKC inhibitor Ro-31-8220 (10 μM).
These results indicate that H_3R activation stimulates the PLC/Ca^{2+}/PKC pathway in a subpopulation of striatal neurons. PLC activation could therefore represent an additional mechanism for histamine to regulate at the post-synaptic level the excitability of striatal neurons.

Disclosures: **N. Rivera-Ramírez:** None. **J. Arias:** None. **U. García-Hernández:** None. **J. Arias-Montaño:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.17/D42

Topic: B.03. G-Protein Coupled Receptors

Support: SNSF grant#31003A-159513/1

Title: Activation of lactate receptor HCAR1 down-modulates neuronal activity in mouse and human brain tissue

Authors: A.-B. ROCHER[1], C. SCHMUZIGER[1], J. WELLBOURNE-WOOD[1], R. DANIEL[2], S. OFFERMANNS[3], *J.-Y. CHATTON[4]
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Abstract: Lactate is a metabolic substrate for neurons that can be provided by astrocytes. The interest in lactate further grew when it was shown that it acts as a neuroprotectant and is important for memory formation. The view of a metabolic pathway as the sole basis for these effects was challenged by the recent discovery of a Gi-protein coupled receptor activated by lactate, named hydroxycarboxylic acid receptor 1 (HCAR1), conferring an additional role of signaling molecule to lactate. We previously showed that activation of HCAR1 by lactate or selective agonists of HCAR1 leads to a concentration-dependent decrease in the activity of mouse cortical neurons in primary culture (Bozzo et al., 2013). In the present study, we investigated both the expression of HCA1R and, for the first time, its activation at the neuronal network level in brain tissue. We found using immunohistochemistry that none of the anti-HCAR1 antibodies tested showed specificity, as they equally stain tissue from HCAR1 knock-out mice. However, we confirmed, using both qRT-PCR and a mouse line expressing mRFP under the HCAR1 promoter, that HCAR1 mRNA transcripts are present in mouse primary neuronal cultures as well as in the mouse brain. The mRFP signal was found to be most prominent in the hilus of the hippocampus, but also present in the CA3, the cerebellum, the brainstem, and the cortex. Excitatory neurons seem to be the main mRFP-positive cell type. At the functional level, application of 3,5-DHBA, a specific HCAR1 agonist, significantly decreased the up-state frequency of spontaneous slow wave oscillations monitored with extracellular field recordings in layer II/III of the entorhinal cortex. 3,5-DHBA agonist application also showed a decrease in neuronal calcium activity in acute slices obtained from tissue resections of human brain. In both cases, neuronal baseline activity was recovered after

washout. These results strengthen the role of lactate as a neuromodulator via HCAR1 activation, and support the hypothesis that down-modulation of spontaneous neuronal activity can be achieved via the activation of HCAR1.

Disclosures: **A. Rocher:** None. **C. Schmuziger:** None. **J. Wellbourne-Wood:** None. **R. Daniel:** None. **S. Offermanns:** None. **J. Chatton:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.18/D43

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant DA035577

Title: Distinct signaling cascades underlie 5-HT6 receptor regulation of neuronal morphology

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Abstract: 5-HT_6 serotonin receptors are promising targets for a variety of cognitive phenotypes and processes, including memory, depression, compulsive and habitual behaviors, and drug reinforcement. Endogenous expression of 5-HT_6 receptors is restricted almost exclusively to the primary neuronal cilia, a small sensory organelle stemming from the cell body of the neuron that senses extra-synaptic signals. Primary neuronal cilia play a critical role in many developmental and psychiatric disorders, including Bardet Biedl Syndrome, Huntington's and Alzheimer's disease, making 5-HT_6 receptors especially promising therapeutic targets. Several distinct signaling pathways mediating 5-HT_6 receptor signaling have been described recently. Here we compared the canonical cAMP-dependent signaling cascade and the other a non-canonical Cdk5/Fyn kinase signaling pathways. Recently we reported that 5-HT_6 receptor antagonism decreases cilia length in primary neuronal cultures, and that drastic overexpression of heterologous 5-HT_6 receptors increases the likelihood for receptor localizing outside of the primary cilia compartment in a dose-dependent fashion; the effects of heterologous overexpression on cilia and neuronal morphology have been controversial. In the present study, we explore the role of 5-HT_6R-dependent signaling on neuronal morphology by restoring 5-HT_6 receptor expression in primary neuronal cultures from 5-HT_6-KO mice, and we found that as we increased the level of receptor expression, we increased the probability that the receptor localized outside of the cilia and generated aberrant and exceedingly long primary cilia. In the subsequent experiments, we picked a moderate level of receptor expression, trying to maintain a more physiological level of expression wherein the receptor localizes exclusively to cilia in >90% of

neurons (as seen with endogenous 5-HT_6R expression). We found that rescue of 5-HT_6R expression is sufficient to increase cilia length and dendritic outgrowth, but primarily in neurons in which the receptor is located exclusively in the primary cilia. Additionally, we found that expression of 5-HT_6R mutants, deficient in agonist-induced cAMP or without the predicted Fyn kinase binding domain, still increase the length of cilia, while the Fyn kinase domain appears to be required for stimulating dendritic outgrowth. Interestingly, 5-HT_6R agonists and antagonists had little effect on dendritic outgrowth and cilia length. Taken together, these findings highlight the complexity of 5-HT_6R function and localization and spotlight the potential risks of altered signaling associated with exogenous overexpression.

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Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: B.03. G-Protein Coupled Receptors

Support: UTMB and Center for Addiction Research

Rising Star award UT system

Title: CRISPR/Cas9-mediated knockout of G-proteins and β-arrestins elucidates their contribution to dopamine D1 receptor signaling

Authors: *M. JAIN[1], B. MONTOYA[1], A. INOUE[2], J. A. ALLEN[1]
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Abstract: Dopamine D1 receptors (D1R) are G protein-coupled receptors (GPCRs) controlling important neurobiological processes including movement, memory and rewarding responses. D1Rs are also drug targets for treating motor deficits in Parkinson's disease and cognitive and motivational deficits in neuropsychiatric diseases. The D1R canonically activates heterotrimeric Gs and Golf G-proteins which, in turn, activate adenylyl cyclase to increase cAMP/PKA signaling and other downstream signaling responses. However, the D1R also engages β-arrestin proteins which independently regulate signaling by controlling receptor internalization and desensitization of G protein-mediated responses. β-arrestins also interact with other signaling proteins such as kinases and can themselves induce an independent wave of GPCR signal transduction. The relative importance of G proteins versus arrestins for controlling the efficacy and duration of D1R signaling remains largely undefined. Here we utilize total knockout of G-

proteins and arrestins in HEK293 cells using CRISPR-Cas9 approaches to define the contribution of these pathways to D1R signaling efficacy and signaling duration. Gs, Golf, all G-proteins or β-arrestin 1/2 were stably knocked-out in HEK293 cells using CRISPR/Cas9 genome editing. Knockout of Gs/olf and β-arrestin 1/2 in parent or knockout cells were validated by western blotting and by measuring Gs/olf-mediated cAMP production using the GloSensor assay. To assess a key node of downstream signaling, D1R-mediated ERK phosphorylation was determined by western blotting. Cell surface expression of an HA-tagged D1R was confirmed using confocal microscopy and internalization assessed by cell surface ELISA. Western blots of Gs/olf and β-arrestin confirmed complete loss of these proteins in knockout cells. No cAMP was generated in the Gs/olf and all G-protein knockout cells in response to D1 or β2AR agonists or cholera toxin. G-proteins and β-arrestin1/2 knockout altered the timing of ERK phosphorylation, with Gs/olf knockout preventing long-lasting p-ERK. β-arrestin 1/2 knockout greatly increased and prolonged the duration of cAMP signaling. This study provides fundamental new insights into mechanisms of D1R signal transduction indicating arrestins limit the intensity and duration of Gs/olf-mediated cAMP signaling while both Gs/olf and arrestins contribute to the activation of ERK phosphorylation. Future studies, including receptor trafficking, temporal studies and unbiased phosphoproteomics will provide a comprehensive understanding of the role of arrestins and Gs/Golf for D1R signaling.

Disclosures: **M. Jain:** None. **B. Montoya:** None. **A. Inoue:** None. **J.A. Allen:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

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Topic: B.03. G-Protein Coupled Receptors

Support: Pharmacological Sciences T32 Predoctoral Training Grant (4T32-GM008602)

NIH Grant R01-NS088413

Title: Regulation of S100A5 expression and secretion by seizure associated receptors GPR37L1 and GPR37

Authors: *T. T. NGUYEN[1], M. M. GIDDENS[1], D. M. DUONG[2], R. A. HALL[1]
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Abstract: Epilepsy is the fourth most common neurological disorder and affects over 65 million people worldwide. Current medications (anticonvulsants) used to treat epilepsy have a number of adverse side effects, and thus it is desirable to identify new drug targets that may allow for the design of novel therapies. A mutation in the G protein-coupled receptor GPR37L1 was recently

found in a large family to be associated with a progressive form of epilepsy in which seizures start around puberty and increase in severity with age, ultimately resulting in death in the late teens to early twenties. Studies from our lab have also revealed that knockout mice lacking GPR37L1 (and/or the closely related receptor GPR37) exhibit greatly increased susceptibility to seizures. To shed light on the potential mechanistic underpinnings of this phenotype, we performed proteomic analyses of whole mouse brain tissue from wild-type vs. GPR37L1/GPR37 double knockout mice to identify proteins regulated by the absence versus presence of these receptors. The single most dramatically downregulated protein in the knockout versus wild-type brain tissue was S100A5, a calcium-binding protein. The reduction of S100A5 expression in the knockout brain tissue was confirmed via Western blot, and co-immunoprecipitation studies revealed GPR37L1 and GPR37 can associate with S100A5. In transfection studies, co-expression of S100A5 with either GPR37L1 or GPR37 resulted in substantially increased secretion of S100A5 from cultured cells. These findings are of interest because several other members of the S100A protein family are known to be secreted to exert neuroprotective actions. Ongoing studies focus on the mechanism by which GPR37L1 and GPR37 can regulate both S100A5 expression levels and secretion.

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Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.21/D46

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant 2 P20 GM103642-06

NIDA Intramural Funds

NSF DBl-1337284

NIGMS-RISE R25 GM061838

Title: Anatomical, biochemical, pharmacological and physiological characterization of functional adenosine A1 and dopamine D1 receptor heteromers in mammalian spinal motoneurons

Authors: M. S. RIVERA-OLIVER[1], E. MORENO[3], Y. ALVAREZ-BAGNAROL[5], C. AYALA-SANTIAGO[2], V. CASADO[4], S. FERRE[6], *M. E. DIAZ-RIOS[7]
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Abstract: Adenosine is a ubiquitous neuromodulator in the central nervous system (CNS), which is involved in numerous functions. More general functions include the regulation of arousal and its role in neuroprotection. The modulatory role of adenosine on dopaminergic transmission depends largely on the existence of antagonistic interactions mediated by specific subtypes of adenosine and dopamine receptors, the so-called A2AR-dopamine D_2 receptor (D2R) and A1R-dopamine D_1 receptor (D1R) interactions. Apart from the endogenous neurotransmitters, these specific adenosine-dopamine receptor interactions seem to be involved in the central effects of caffeine, a non-selective A1R-A2AR competitive antagonist and the most consumed psychoactive drug in the world. We have recently found a significant antagonistic interaction between A1R and D1R ligands in the mouse spinal cord that mediates the ability of caffeine to produce locomotor activation by acting on spinal circuits, although the molecular mechanisms and cellular localization remained to be determined. In the present study, A1R-D1R heteromerization is first demonstrated in mammalian transfected cells using biophysical techniques. Synthetic peptides with the amino acid sequence of specific transmembrane domains (TMs) of the D1R provided the tool to demonstrate that the antagonistic interaction between A1R and D1R ligands depends on A1R-D1R heteromerization and allowed the specific identification of A1R-D1R heteromers in spinal motoneuron, where they mediate the spinal modulatory control by adenosine and dopamine and the strong spinal pharmacological effects of caffeine. These results can have important implications for the pharmacotherapy of spinal cord injury (SCI).

Disclosures: M.S. Rivera-Oliver: None. **E. Moreno:** None. **Y. Alvarez-Bagnarol:** None. **C. Ayala-Santiago:** None. **V. Casado:** None. **S. Ferre:** None. **M.E. Diaz-Rios:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.22/D47

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Gpr110 conformational change upon synaptamide binding probed by in-cell crosslinking and mass spectrometry

Authors: B. HUANG[1], J.-W. LEE[1], *H.-Y. KIM[2]
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Abstract: The adhesion G-protein coupled receptor 110 (GPR110, ADGRF1) has been recently deorphanized as a target receptor for *N*-docosahexaenoylethanolamine (synaptamide), an

endogenous metabolite of docosahexaenoic acid (DHA, 22:6n-3) that is essential for proper brain development. The synaptamide binding to GPR110 induces cAMP production and promotes neurite growth and synaptogenesis. To understand the molecular basis of the activation of GPR110, we probed the conformation of GPR110 and synaptamide-induced conformational changes using in-cell chemical crosslinking and quantitative mass spectrometry. HEK cells overexpressing human GPR110-HA were treated with synaptamide or oleoylethanolamide as a control followed by a lysine-specific cross-linker, disuccinimidyl suberate (DSS), for in-cell crosslinking. The DSS-modified GPR110 was pulled-down with anti-HA antibody and eluted with HA peptide. The sample was subjected to SDS-PAGE, in-gel reduction/alkylation, and tryptic digestion. The resulting peptides were analyzed by nanoLC-ESI-MS/MS, and the crosslinked peptides were identified by xQuest software and quantified by Progenesis QI for Proteomics. A total of 18 intra-molecularly crosslinked lysine pairs were identified in the extracellular *N*-terminal region of GPR110 which contains a conserved GAIN domain. Among them, K29-K38, K151-K73, K187-K240, K240-K254, K398-442, K398-K438, K398-K427, K427-K442, K427-K438, and K151-K442, resulted from through-space crosslinking between two peptide segments. In addition, a through-space crosslinking between the intracellular loop III and the C-terminal (K783-K852) were identified. The α-carbon distance between the lysine pair in each crosslinked peptide detected above is within ~24 Å, the maximum crosslinking length of DSS. After synaptamide stimulation, the cross-linking of K398-K438 in the GAIN domain and the inter-intracellular domain cross-linking of K783-K852 increased significantly compared to the oleoylethanolamide control, suggesting that the lysine residues in these crosslinked pairs moved closer to each other, increasing cross-linking opportunity. Our data indicated that GAIN domain conformational changes occur upon synaptamide binding to the receptor. Moreover, synaptamide affected the local intracellular configuration involving the intracellular loop III and the C-terminal, suggesting a significant role of synaptamide in the interaction of GPR110 with G proteins for downstream signaling for neurodevelopmental control.

Disclosures: **B. Huang:** None. **J. Lee:** None. **H. Kim:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.23/D48

Topic: F.02. Behavioral Neuroendocrinology

Title: Generation of cell lines with stable expression of the orphan GPCR GPR101: New tools for ligand screening and for the identification of deregulated pathways

Authors: *G. TRIVELLIN[1], M. M. JANJIC[2], D. O. LARCO[3], M. TOMIC[2], A. F. DALY[4], L. PALMEIRA[4], F. R. FAUCZ[1], A. BECKERS[4], T.-Y. J. WU[3], D. CALEBIRO[5], S. S.

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Abstract: Background and Aims: GPR101 is an orphan G protein-coupled receptor (GPCR) that is duplicated in patients with X-linked acrogigantism (X-LAG) syndrome and over-expressed in their growth hormone (GH)- and prolactin (PRL)-secreting tumors. GPR101 is a constitutively active GPCR that strongly activates the cAMP pathway. To elucidate the mechanisms through which GPR101 causes GH over-secretion we generated HEK293 and GH/PRL-secreting (GH3) cells with stable GPR101 expression. Methods: Both cell lines were created via direct integration of a human *GPR101*-coding sequence into their genome. GPR101 expression was quantified by RT-qPCR and immunofluorescence/western blotting. Cell proliferation (MTT assay), cAMP levels (^{125}I-labeled cAMP tracer), and calcium signaling (FURA 2 AM) were determined. RNA was extracted from both cell lines and subjected to RNA-seq. Differential gene expression between control and GPR101-expressing cells and pathway analysis was carried out. De-regulated genes were validated by RT-qPCR. Results: High GPR101 expression was achieved in both cell lines and confirmed at the mRNA and protein level. *GPR101*-expressing cells proliferated at different rates from the respective controls: GPR101-HEK293 cells were slow-dividing, while GPR101-GH3 divided faster. cAMP production was enhanced in GPR101-GH3 and accompanied by increased excitability of cells. Differential expression analysis in HEK293 cells revealed several up-regulated and few down-regulated genes. Among the genes with high expression, several were linked to the cAMP pathway: *CGA*, *PCK1*, *LINC00473* and *PDE3A*. Enrichment analysis ranked cytoskeleton remodeling and cell cycle regulation (inhibition of G1/S transition) as the most relevant pathways. In GH3 cells most of the genes with a significantly different expression encoded for cytoskeletal (*Actn2*, *Nefl*) and membrane-localized proteins (*Dcn*, *Nrg1*, *Kcnj1*, *Trhr*, *Adgrb1*, *Syt4*). Biological processes associated with these genes are: vesicle transport and fusion, cytoskeleton organization, and energy homeostasis. Conclusions: These results show that the intrinsic activity of GPR101 strongly stimulates cAMP production and this in turn facilitates voltage-gated calcium influx. Changes in cAMP/calcium signaling are accompanied with faster/slower cell division depending on the cell type. Accordingly, several genes associated with these and related pathways are differentially expressed. The establishment of these cell lines will be of paramount importance to validate putative GPR101 ligands and to conduct functional studies.

Disclosures: G. Trivellin: None. **M.M. Janjic:** None. **D.O. Larco:** None. **M. Tomic:** None. **A.F. Daly:** None. **L. Palmeira:** None. **F.R. Faucz:** None. **A. Beckers:** None. **T.J. Wu:** None. **D. Calebiro:** None. **S.S. Stojilkovic:** None. **C.A. Stratakis:** None.

Poster

038. GPCRs: 5-HT, mGlu, and Other Metabotropic Receptors

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 038.24/D49

Topic: E.03. Basal Ganglia

Support: Consejo Nacional de Ciencia y Tecnología, Grant 220448 to J.-A. A.-M.

Consejo Nacional de Ciencia y Tecnología, Doctorate scholarship to G. N.-A..

Consejo Mexiquense de Ciencia y Tecnología, Doctorate scholarship to G. N.-A..

Title: Human RGS9-2 protein regulates the cell signaling elicited by the human histamine H_3 receptor expressed in human embryonic kidney HEK-293T cells

Authors: *G. NIETO-ALAMILLA, JR[1], J. ESCAMILLA-SÁNCHEZ[2], J. ARIAS-MONTAÑO[2]
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Abstract: The regulators of GPCR signaling (RGS) family proteins accelerate the hydrolysis of GTP by the α subunits of G proteins and modulate thus the intracellular effects elicited by GPCR activation. The striatal medium spiny neurons co-express RGS9-2 and histamine H_3 receptor isoforms (H_3Rs), which couple to $G\alpha_{i/o}$ proteins. In this work we compared the effect of over-expressing the human RGS9-2 protein (hRGS9-2) on G protein activation and signaling induced by the stimulation of the co-transfected human H_3R of 445 amino acids (hH_3R), the originally cloned receptor and the most abundantly expressed in the human brain.
Human embryonic kidney cells (HEK-293T) were transiently transfected with the hH_3R along with the hRGS9-2 protein or mock plasmid. The effect of hRGS9-2 on the capability of hH_3Rs to activate $G\alpha_{i/o}$ proteins and trigger intracellular signaling was evaluated by measuring [^{35}S]-GTPγS binding to cell membranes, and forskolin-induced cAMP accumulation and phosphorylation of Erk1/2 proteins in intact cells.
Maximal specific binding (Bmax) of [^{3}H]-N-methyl histamine to cell membranes was 468 ± 12 and 442 ± 38 fmol.mg^{-1} protein for HEK-293T-hH_3R and HEK-293T-hH_3R/hRGS9 cells, respectively, with similar dissociation constants (Kd, 2.57 nM and 3.38 nM). Activation of the hH_3R with immepip increased [^{35}S]-GTPγS binding in both cells with no difference in the maximum effect (146.3 ± 4.4% and 150.0 ± 5.3% of basal, respectively) or potency (pEC_{50}, 8.57 ± 0.26 and 9.00 ± 0.33). Over-expression of hRGS9-2 reduced significantly the maximum inhibition of cAMP accumulation elicited
by hH_3R activation (-37.7 ± 5.1% and -19.2 ± 5.3% of control values for HEK-293T-hH_3R and HEK-293T-hH_3R-hRGS9 cells, respectively), with no difference in the agonist potency. Over-

expression of hRGS9-2 increased by 54% the basal phosphorylation of Erk1/2, independently of the activation of the hH_3R.
These results indicate that in HEK-293T cells hRGS9-2 reduces hH_3R_{445} signaling and up-regulates the MAPK pathway in a receptor-independent manner.

Disclosures: G. Nieto-Alamilla: None. **J. Escamilla-Sánchez:** None. **J. Arias-Montaño:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 039.01/D50

Topic: B.07. Synaptic Transmission

Support: NS02206132

Title: Alterations to entorhinal cortex cholinergic circuits in cognitive decline

Authors: *M. ANANTH[1], D. A. TALMAGE[2], L. W. ROLE[3]
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Abstract: Age-related cognitive decline is a growing problem. By the year 2050, over 80 million people in the United States will be aged 65 and over, and thus our understanding of the pathophysiology and progression of age-related cognitive decline is of the utmost importance. The entorhinal cortex (EC) is a parahippocampal region that is known to be particularly vulnerable in aging and pathological aging. The EC receives extensive cholinergic input from the basal forebrain cholinergic nuclei (BF), and this input is dramatically reduced in pathological aging conditions. Using a mouse model that recapitulates aging pathology at an accelerated timescale (5xFAD x $NOS2^{-/-}$), we find that performance on a cholinergic dependent task that engages the entorhinal cortex is impaired. Electrophysiological analysis of the BF- EC circuit in WT vs age-accelerated mice with optogenetically tagged cholinergic inputs, and high resolution brain mapping techniques reveal circuit level and anatomical alterations to the BF-EC circuit at the onset of cognitive decline.
EC neurons in control mice typically fire at low frequencies; activation of cholinergic inputs increases firing rate in these mice. In contrast, EC units in our aging model have elevated basal firing rate. Furthermore, opto-stimulation of cholinergic inputs to EC neurons in the aging model elicits little to no change in firing rate. In investigating the mechanism for this impaired responsiveness, we found that there is a dramatic and significant loss of cholinergic input to the EC in our aging mouse model. Given the recent shift in focus from cholinergic nuclei to the importance of their axonal arbors, we postulate that the cognitive impairment in EC based tasks

may be due to a dramatic shift in cholinergic tone in the EC, that results in imbalanced ratio of excitation to inhibition. To test this hypothesis, we are examining the effect of decreasing cholinergic tone on EC activity in the control vs aging mouse model. Parallel studies in humans using PET and a marker that targets cholinergic synapses, have been initiated to test whether EC specific cognitive impairments in humans also track to the loss cholinergic input to the EC, as they do in the mouse model. By comparing across species and analytic modalities, these studies should provide valuable insight into the circuit mechanisms underlying cognitive decline as it pertains to EC related deficits in performance.

Disclosures: M. Ananth: None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 039.02/D51

Topic: B.07. Synaptic Transmission

Support: NIH Grant MH104638

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Title: Cholinergic modulation of plasticity in the basolateral amygdala

Authors: *S. C. TRYON, L. LIU, K. F. KAIGLER, A. J. MCDONALD, M. A. WILSON, D. D. MOTT
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Abstract: The basolateral amygdala (BL) is implicated in fear memory consolidation and fear memory extinction. The BL receives afferent projections from brain regions within the fear network, including projections from the prelimbic cortex (PL). The BL also receives dense cholinergic input from the basal forebrain. We have previously shown that muscarinic acetylcholine receptors (mAChRs) on terminals of PL neurons inhibit PL input onto pyramidal neurons (PNs) of the BL. However, it remains to be understood how this presynaptic inhibition regulates plasticity at these synapses or correlates with fear extinction behaviors. Using brain slice electrophysiology, we found that activation of mAChRs with muscarine (10 uM) inhibited PL input to BL PNs and that the extent of inhibition varied significantly between individuals. Although muscarine suppressed PL input during a single stimulus, it increased the reliability of

excitatory transmission during a stimulus train by reducing synaptic depression. This effect was greatest at stimulus frequencies in the gamma band (30-90 Hz), suggesting that PL signals arriving at gamma frequencies would be strengthened during periods of high cholinergic tone. Furthermore, it was found that gamma-frequency stimulation induced LTP at these PL-BL synapses that was markedly enhanced by mAChR activation. Thus, mAChRs play an important role in glutamatergic neurotransmission and plasticity at these PL inputs to BL that are involved in fear extinction learning. We have previously shown that outbred Long-Evans rats show individual differences in extinction of freezing behavior in response to a conditioned cue (tone). Since we also saw individual variation in muscarinic inhibition of PL input, we investigated whether the extent of muscarinic inhibition at BL synapses examined ex vivo was correlated with individual differences in extinction learning seen in vivo. Our findings indicate that the extent of mAChR inhibition of PL input to the BL is correlated with extinction learning. These results suggest a mechanistic role for cholinergic regulation of the individual variation in fear extinction and implicate muscarinic receptors as therapeutic targets for fear disorders.

Disclosures: **S.C. Tryon:** None. **L. Liu:** None. **K.F. Kaigler:** None. **A.J. McDonald:** None. **M.A. Wilson:** None. **D.D. Mott:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

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Program#/Poster#: 039.03/D52

Topic: B.07. Synaptic Transmission

Support: NIH DA0171088 (ALB)

NIH NS088958 (ALB)

McKnight Foundation (ALB)

Title: Cholinergic modulation of PV interneuron activity in sensory neocortex

Authors: *S. E. MYAL[1], J. URBAN CIECKO[2], A. L. BARTH[3]
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Abstract: Acetylcholine (ACh) regulates cortical circuits important for attention and sensory encoding, and elevated ACh is associated with network desynchronization and increased inhibition. Prior studies in mice suggest that ACh differentially changes the firing rates of parvalbumin (PV) and other interneurons, and that pharmacologic manipulations of cholinergic receptor activity may have different effects from endogenously released ACh.
To examine cholinergic effects on PV neuron intrinsic properties, we performed whole-cell

recordings in acute brain slices of barrel cortex in ChAT-ChR2/PV-Cre transgenic mice. Application of carbachol, a broad-spectrum cholinergic agonist, depolarized layer 2/3 PV cells by 3-5mV and increased their spontaneous firing rates. In contrast, endogenous ACh release (via optogenetic activation of cortical afferents) did not change resting membrane potential or firing frequency at either minimal (single-pulse, 10msec) or prolonged fiber activation (50 x 10msec pulses at 50Hz) at frequencies spanning the range of cholinergic cell activity in awake animals. We further compared the effects of endogenous versus pharmacologic ACh receptor activation on excitatory inputs to PV neurons. Carbachol increased the amplitude of excitatory postsynaptic potentials (EPSPs) by up to 3-fold in synaptically connected pyramidal-to-PV pairs in layer 2/3. In contrast, optogenetically-induced endogenous ACh release did not change EPSP amplitude irrespective of stimulus strength (1-50 pulses, 0.2-50Hz).
Thus, we find that PV cell activity and excitatory drive from pyramidal cells are enhanced by cholinergic agonist drugs, but not endogenous ACh. This suggests that *in vivo* cortical desynchronization by acetylcholine may occur via increased activity of other inhibitory neuron types, either by enhancement of intrinsic excitability or by direct or indirect modulation of excitation-inhibition ratios in the cortical network.

Disclosures: S.E. Myal: None. **J. Urban Ciecko:** None. **A.L. Barth:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

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Program#/Poster#: 039.04/D53

Topic: B.07. Synaptic Transmission

Support: NRF (National Research Foundation of Korea) Grant funded by the Korean Government (NRF-2016-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program)

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3.This research was supported by the Brain Research Program (NRF-2015M3C7A1028790) through the National Research Foundation (NRF) of Korea funded by the Ministry of Science, ICT and Future Planning.

Title: Differentialfeedforward and feedback inhibition recruitment by acetylcholine controls thehippocampal CA1 pyramidal cell’s input-output function through endocannabinoid activation

Authors: *K. PARK, ***K. PARK**, J. KWAG
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Abstract: Spikes of CA1 pyramidal cell (PC) are the final output signal of the hippocampus. Thus, investigating how CA1 PC transforms different frequencies of synaptic inputs from CA3 PC into spike outputs in Input/Output (I/O) function can help elucidate hippocampal information processing. We previously demonstrated that CA1 PC I/O function is dependent on the synaptic input layers (stratum oriens (SO) and stratum radiatum (SR)) through which CA3 inputs are received and that such input layer-dependence is achieved via differential recruitment of feedforward (FF) and feedback (FB) inhibition in these layers. In fact, interneurons in SO and SR layers are strongly modulated by acetylcholine (ACh), but how ACh modulates FF and FB inhibition in different synaptic input layers to control the CA1 PC I/O function is poorly understood. By stimulating CA3 PC axons in either SO or SR layer at 1 - 30 Hz and recording the corresponding firing rate of CA1 PC in in vitro whole-cell patch-clamp recordings, we show that ACh receptor agonist (CCh, 50 μM) selectively increases the slope of I/O function (gain) in response to SO stimulation (Control: 7.64 ± 0.74, n =9 vs CCh: 11.67 ± 0.87, n = 10, $p < 0.01$), but not SR (Control: 2.79 ± 0.68, n = 9 vs CCh: 3.37 ± 0.37, n = 10, $p > 0.05$). Interestingly, such CCh-mediated gain modulation in SO layer was inhibited by GABAA receptor antagonist (GABAZINE, 2 μM), indicating that CCh selectively modulated the GABAA receptor-mediated inhibition only in SO layer. To see whether FF or FB was modulated by CCh, we investigated the probability of FF and FB IPSC recruitment onto CA1 PC in response to SO and SR stimulation. CCh facilitated FB IPSC probability (Control: 0.69 ± 0.11 vs CCh: 1.00 ± 0.00, n = 6, $p < 0.05$), while suppressed FF IPSC probability in response to SO stimulation (Control: 0.69 ± 0.07 vs CCh: 0.11 ± 0.11, n = 6, $p < 0.01$). In contrast, SR stimulation recruited only FF IPSC in both control and CCh conditions (Control: 1.00 ± 0.00 vs CCh: 0.95 ± 0.05, n = 4, $p > 0.05$), suggesting that CCh-mediated preferential facilitation of FB and suppression of FF inhibition in SO layer may account for the CCh-mediated gain modulation. Since CCh is known to activate endocannabinoid (eCB), a retrograde neurotransmitter reducing GABA release, we tested whether CCh-activated eCB is involved in the CCh-modulation of gain using cannabinoid-1-receptor antagonist (AM251, 10 μM) in the presence of CCh. Indeed, AM251 blocked the CCh-mediated gain modulation (CCh + AM251: 8.00 ± 1.17, n =9, one-way ANOVA, control vs CCh + AM251: $p > 0.05$, CCh vs CCh + AM251, $p < 0.05$), demonstrating that ACh enables dynamic modulation of CA1 PC's I/O function via eCB-mediated change of FF and FB inhibition recruitment.

Disclosures: K. Park: None. **J. Kwag:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 039.05/D54

Topic: B.07. Synaptic Transmission

Support: NIH Intramural Research Program

Title: Hippocampus and entorhinal cortex recruit cholinergic- and NMDA receptor- dependent mechanisms separately to generate theta oscillations

Authors: *Z. GU, J. L. YAKEL
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Abstract: It has long been known that there are atropine-sensitive and atropine-resistant components of hippocampal theta oscillations; the latter is suspected primarily to be NMDA receptor-dependent. However, the sites of cholinergic receptor and NMDA receptor activation, and how they contribute to theta generation, are largely unknown. With a septo-entorhinal-hippocampal brain slice tri-culture preparation, our recent study suggested that NMDA receptors in the entorhinal cortex (EC) were critical for theta expression in the EC hippocampal network. Here we observed that cholinergic receptors in the hippocampus were critical for theta generation in the same *in vitro* preparation. We then validated the locations of the active cholinergic and NMDA receptors involved in theta generation *in vivo*. We recorded hippocampal theta oscillations from mice freely moving in an open field, with cholinergic or NMDA receptor antagonists infused to either the hippocampus or EC before the *in vivo* theta recordings. Consistent with our *in vitro* observations, we observed that cholinergic receptor antagonists significantly reduced hippocampal theta power when infused to the hippocampus but not to EC. On the other hand, NMDA receptor antagonist significantly reduced hippocampal theta power when infused to EC but not to the hippocampus. Theta oscillations are strongly suggested to support spatial memory. We further examined the effects of these receptor antagonists on spatial working memory with the Y-Maze spontaneous alternation test. Consistent with their localized effects on theta power, cholinergic receptor antagonists significantly impaired Y-Maze alternation when infused to the hippocampus, while NMDA receptor antagonist significantly impaired Y-Maze alternation when infused to EC. These results thus strongly suggest that EC and hippocampus both actively contribute to theta generation but through separate mechanisms. Meanwhile our *in vitro* preparation should continue to provide a valuable platform in further exploring the detailed cellular mechanisms in hippocampal and EC circuits in theta generation.

Disclosures: Z. Gu: None. **J.L. Yakel:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: B.07. Synaptic Transmission

Support: NIH Intramural Research Program ES090089

Title: Cholinergic-GABAergic interactions in the hippocamposeptal pathway

Authors: *J. C. DAMBORSKY, J. L. YAKEL
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Abstract: A subset of GABAergic neurons in the hippocampus send projections to the medial septum/diagonal band of Broca (MS/DBB) region of the basal forebrain. These hippocamposeptal (HS) projection neurons are part of a reciprocal circuit that is critical for mediating spatial and episodic memory, and is disrupted in Alzheimer's disease (AD). Previous studies have shown that HS neurons form functional connections with neurons in the MS/DBB, however, there is still little known about how HS neuronal activity is integrated into this circuit. Here, we sought to isolate and study how HS output impacts and is impacted by cholinergic signaling in the MS/DBB. To examine how HS synaptic transmission is modulated in the MS/DBB, we used optogenetics to selectively stimulate HS terminals while performing whole-cell patch clamp recordings from MS/DBB neurons in acute slices. Most HS neurons co-express somatostatin (SST), so to target these neurons we performed stereotaxic injections of AAV containing mCherry/channelrhodopisin-2 (ChR2) into the hippocampus of SST-Cre mice. This resulted in specific expression of mCherry and ChR2 in SST+ neurons in the hippocampus, and extensive expression of mCherry/ChR2-containing fibers in the MS/DBB. Activation of these HS terminals using 470 nm light stimulation resulted in light-induced synaptic inhibitory postsynaptic currents (IPSCs) in both cholinergic and GABAergic neurons in the MS/DBB. Bath application of the acetylcholine receptor agonist carbachol (50 μM) significantly decreased the amplitude of these light-evoked IPSCs, suggesting that HS GABAergic transmission in the MS/DBB is modulated by cholinergic activity. We next wanted to record from HS neurons that synapse onto cholinergic neurons in the MS/DBB to determine how the excitability of these neurons is impacted by activity within the hippocampus. To do this, we performed monosynaptic retrograde synaptic tracing by injecting a Cre-dependent AAV helper virus and glycoprotein-deleted rabies virus that contained ChR2/mCherry directly into the MS/DBB of ChAT-Cre mice. We were then able to record from the mCherry/ChR2-expressing neurons in the hippocampus that form direct synaptic connections with cholinergic neurons in the MS/DBB. Using this method, we will determine how the excitability of HS neurons that synapse onto cholinergic neurons in the MS/DBB is regulated. In conclusion, we have determined that GABAergic and cholinergic activity in the HS pathway is intertwined in a bidirectional manor. Future studies will reveal the importance of these cholinergic-GABAergic interactions for memory formation, and the extent to which this circuit is disrupted in AD.

Disclosures: J.C. Damborsky: None. **J.L. Yakel:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 039.07/D56

Topic: B.07. Synaptic Transmission

Support: Alzheimer's Association (KM)

NIH AG047652 (WHG)

Title: Quantal analysis of basal forebrain GABAergic synapses of vGAT ChR2-eYFP BAC mice using minimal optogenetic stimulation in a reduced synaptic preparation

Authors: *K. S. MONTGOMERY, D. W. DUBOIS, A. S. FINCHER, E. A. BANCROFT, E. A. MIGUT, W. H. GRIFFITH
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Abstract: Our lab is studying GABAergic (gamma-aminobutyric acid) synaptic transmission in the rodent basal forebrain (BF) to better understand the relationship between age-related synaptic dysfunction and cognitive impairment. Synaptic dysfunction is part of the initial pathology of Alzheimer's disease in humans and is detected prior to cognitive impairment in animal models of brain aging. We have shown that frequency, but not amplitude, of spontaneous GABAergic inhibitory postsynaptic currents (IPSCs) are reduced in BF cholinergic cells of aged, cognitively impaired rats (Griffith et al., J. Neurophysiol. 111:27-286, 2014). These data suggest a dysfunction of presynaptic GABAergic transmission during aging. To test this hypothesis directly, we are investigating pre- and postsynaptic parameters of synaptic transmission using quantal analysis in a reduced synaptic preparation of BF neurons with minimal optogenetic light (470 nm) stimulation. Whole-cell patch clamp electrophysiology was used in young (2-6 mo) vGAT ChR2(H134)-EYFP BAC transgenic mice (channelrhodopsin expression under control of promotor for vesicular GABA transporter, specific to GABAergic neurons). The reduced synaptic preparation consists of BF neurons acutely dissociated without enzyme treatment. Such neurons retain presynaptic terminals that can be stimulated with light on soma and proximal dendrites. Light-evoked IPSCs were analyzed by the Variance-Mean method for quantal analysis (Clements and Silver, 2000), the method of failures and the coefficient of variance method for calculations of quantal content (m). Comparable results were obtained for m-values using the method of failures (m= 0.48, 0.924 and 1.513 in 1 mM, 2 mM, and 4 mM external calcium concentrations [Ca], respectively n= 2-11) and the coefficient of variance method (m= 0.62, 0.93 and 1.52 in 1 mM, 2 mM, and 4 mM [Ca] respectively, n= 3-6). Baclofen(30 μM), a GABAB receptor agonist that inhibits presynaptic voltage gated calcium channels, decreased m-values in 2 mM [Ca] from 0.95$\pm$0.15 in control, to 0.48 $\pm$0.12 in baclofen, recovering to 1.11$\pm$ 0.31 after washout (n=6, p=0.041). These data demonstrate that the optogenetic mouse model along with

different methods of quantal analysis can be used for investigation of synaptic function. Similar studies using aged (18-24 mo) mice are in progress. Alzheimer's Association Grant (KSM) NIH grant AG047652 (WHG)

Disclosures: K.S. Montgomery: None. **D.W. DuBois:** None. **A.S. Fincher:** None. **E.A. Bancroft:** None. **E.A. Migut:** None. **W.H. Griffith:** None.

Poster

039. Cholinergic Modulation

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Topic: B.07. Synaptic Transmission

Support: McKnight Foundation

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Title: Precisiely-timed presynaptic nicotinic receptors activation drives SST interneurons in neocortical circuits

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Abstract: Inhibition through somatostatin (SST) neurons is a powerful potential mechanism for gain control in neocortical circuits, and it has been widely investigated in both experimental and computational studies. Approximately 50% of all pyramidal neurons are connected to a nearby SST neuron. However, these inputs are remarkably ineffective, with synaptic failures that occur in more than 70% of all stimulus trials. Here, we sought to determine the conditions under which the brain makes use of this ubiquitous synaptic motif. We used a combination of pharmacological screening, optogenetic activation of specific modulatory pathways, and paired

whole-cell recordings from layer 2/3 pyramidal-SST pairs in brain slices and in vivo in the barrel cortex of a mouse to examine how synaptic inputs can be altered. Pharmacological screening of neuromodulatory pathways revealed that cholinergic agonists uniquely enhance synaptic efficacy of pyramidal-SST connections. Brief, optogenetically-gated stimulation of cholinergic fibers in the neocortex dramatically enhanced pyramidal to SST input. These effects were mediated by presynaptic nicotinic receptors and the activation of PKA signaling pathways at Pyr-SST inputs, and require a delay between cholinergic release and the enhancement of release probability. Moreover, we found that these effects were synapse-specific and did not occur at local excitatory connections between pyramidal neurons, indicating that cholinergic modulation selectively re-weights synaptic transmission toward enhanced inhibition from SST neurons. Brain state and synapse-specific unmasking of ubiquitous connection motifs may be a powerful way to functionally rewire cortical circuit dependent on behavioral demands.

Disclosures: J. Urban Ciecko: None. **J. Jouhanneau:** None. **J.F.A. Poulet:** None. **A.L. Barth:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 039.09/D58

Topic: B.07. Synaptic Transmission

Title: Modulation of synaptic transmission using muscarinic and GABA-A receptor ligands in neuronal cultures using a high capacity assay

Authors: *J. SVENSSON DALÉN[1], C. LINDWALL-BLOM[1], Å. JÄGERVALL[1], M. KARLSSON[1], P. KARILA[1], S. A. NEALE[2], T. E. SALT[2]
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Abstract: Modulators of synaptic transmission, acting at various molecular targets, have great potential for development as novel therapeutic agents in an extensive range of CNS diseases, and the search for novel specific pharmacological agents is of widespread interest. However, traditional high throughput screening approaches primarily rely on heterologous expression systems which lack the ability to replicate synaptic complexity. Thus there is a need to develop screening systems that can evaluate compounds on measures of synaptic transmission. Here, in a 96-well format, we used Cellaxess Elektra® electric field stimulation (EFS) to excite cultured mouse cortical neurones loaded with the calcium fluorophore Calcium 5 in an imaging based microplate reader. By simultaneously electrically stimulating a discrete subset of the neurones in each well we recorded transient, synaptically mediated calcium elevations in neurones away from the stimulating field. These responses were mediated by AMPA and NMDA receptors, as evidenced by concentration dependent block by NBQX and MK801, respectively. We have

studied the effects of compounds acting at either muscarinic receptors or GABA-A receptors as examples of agents that can modulate synaptic transmission via G-protein coupled receptors (GPCRs) or ligand-gated ion channels (LGICs).
Addition of the broad-spectrum muscarinic agonist carbachol to the cultures resulted in a concentration-related reduction of synaptic transmission, with an EC_{50} of 2.2 µM - a value that is similar to the EC_{50} observed for the reduction of synaptic transmission in the CA1 area of the mouse hippocampal slice. The effect of carbachol could be reduced by the selective M1 receptor antagonist VU0255035. In separate experiments, addition of the GABA-A agonist muscimol or the GABA-A modulator allopregnanolone resulted in concentration-related reductions of synaptic transmission, with EC_{50} of 0.5 µM and 0.1 µM respectively. These results show that it is possible to evaluate the modulation of synaptic transmission in cultured neurones using a 96-well plate format and that this produces results comparable to those obtained in electrophysiological studies. Furthermore, this approach can be successfully used in studies of agents acting at GPCRs and LGICs.

Disclosures: **J. Svensson Dalén:** A. Employment/Salary (full or part-time):; Cellectricon AB. **C. Lindwall-Blom:** A. Employment/Salary (full or part-time):; Cellectricon AB. **Å. Jägervall:** A. Employment/Salary (full or part-time):; Cellectricon AB. **M. Karlsson:** A. Employment/Salary (full or part-time):; Cellectricon AB. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB. **S.A. Neale:** A. Employment/Salary (full or part-time):; Neurexpert Ltd. **T.E. Salt:** A. Employment/Salary (full or part-time):; Neurexpert Ltd.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 039.10/D59

Topic: B.07. Synaptic Transmission

Support: Biogen

Title: Enantiomer specific properties of solifenacin in the central nervous system

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Abstract: Solifenacin (VESIcare®, solifenacin succinate), an anti-muscarinic compound, has recently drawn significant interest from the scientific community. Though currently approved by the Federal Drug Administration (FDA) for the treatment of peripherally-mediated symptoms of overactive bladder (OAB), central nervous system (CNS) penetrance has also been documented[1]. Additionally, increased myelin content in a hypomyelinated mouse model following systemic

administration has been demonstrated[2]. However, somewhat conflicting data were published earlier this year from a phase II clinical trial suggesting that co-administration of Solifenacin permitted higher amounts of Donepezil, a cholinesterase inhibitor used to improve memory in Alzheimer's disease patients, to be administered with reduced side-effects[3]. This effect was attributed to Solifenacin's poor blood-brain barrier (BBB) penetration[3]. In order to assess the CNS penetrance of Solifenacin, we utilized a pharmacologically-inducible hypothermia mouse model as previously described[4]. Systemic administration of (S,R)-Solifenacin (0.3-30mg/kg) was incapable of blocking centrally-mediated hypothermia induced by administration of the muscarinic agonist Pilocarpine (15mg/kg). In contrast, the more active enantiomer, (R,R)-Solifenacin (0.3-30mg/kg), administered by the same route, demonstrated a dose-dependent blockade of the hypothermic response. Autoradiographical competition experiments in mouse brain tissue sections using 0.4 nM [^{3}H]N-methylscopolamine demonstrated a much lower binding affinity of (S,R)-Solifenacin as compared to (R,R)-Solifenacin. Although our data obtained from the hypothermia assay suggested that (S,R)-Solifenacin was incapable of crossing the BBB, our autoradiography data raised the additional question that (S,R)-Solifenacin might have been ineffective in the hypothermia assay due to its low binding affinity. Further work is required to resolve the differences in BBB permeability of (S,R)- and (R,R)-Solifenacin and determine what disease indications would benefit the most from these molecules.

Disclosures: J. Archbold: A. Employment/Salary (full or part-time):; Biogen. **R. Hargreaves:** None. **S. Patel:** None.

Poster

039. Cholinergic Modulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 039.11/D60

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIAAA Grant 5R01AA021775-04

Title: Behavioral but not neurochemical alterations in the functional assessment of cholinergic parameters of ChAT::CRE rats

Authors: *J. M. HALL, L. M. SAVAGE
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Abstract: The development of genetically modified mice has advanced the field of neuroscience, but the development of genetically modified rats has lagged significantly behind. To date, no studies have assessed whether the ChAT::CRE rats, relative to their wild-type counterparts (Long-Evans) display normal spatial performance associated behavioral-elicited acetylcholine (ACh) release. ChAT::Cre rats and nongenetically modified Long-Evans rats

(wild-type) were tested on a spontaneous alternation task and ACh levels in the hippocampus and frontal cortex were measured during maze testing. Results indicated that ChAT::CRE rats have a lower level of spontaneous alternation performance ($p<0.003$; 42% [wildtype] vs. 33%[ChAT::Cre]) compared to the wild-type rats. However, both hippocampal and prefrontal cortical ACh efflux was similar between ChAT::CRE and wild-type rats: there were significant increases, relative to baseline, in both the frontal cortex (227% vs 232%) and hippocampus (190% vs 199%) in ACh efflux in both types of rats during spontaneous alternation. Future investigation should determine whether any differences exist in the number of cholinergic markers between ChAT::CRE and wild-type rats. These data advocate that some caution should be employed when using the ChAT::CRE rat line for behavioral assessment.

Disclosures: J.M. Hall: None. **L.M. Savage:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.01/D61

Topic: B.08. Synaptic Plasticity

Support: Young Investigator Grant (25118)- Brain and Behavior Foundation

Title: Role of the endocannabinoids in amygdala synaptic competition

Authors: N. MADEIRA, *R. FONSECA
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Abstract: The synaptic-capture hypothesis of memory allows weak events, only capable of inducing transient, short-term memories, to be consolidated into long-term memories if occurring in the context of other strong events. Memory cooperation is presumably achieved by the sharing of a common pool of plasticity-related proteins (PRPs) that are captured by synaptic tags, set at activated synapses.Interestingly, memories can also compete, interfering with each other. What are the rules that determine whether memories cooperate or compete? To tackle this question, we have studied the interaction between the cortical and thalamic afferents to projection neurons of the lateral amygdala (LA), a circuitry necessary for the formation of fear memories. We found that cortical synapses can cooperate with thalamic synapses, even within an extended time window of 30 minutes. Thalamic-cortical cooperation is dependent on the sharing of PRPs between the two groups of activated synapses and results in the re-enforcement of both inputs in an associative manner. Interestingly, synaptic cooperation between the cortical and thalamic synapses is bi-directional but temporally asymmetrical.The time window of thalamic cooperation is limited by the activation of the endocannabinoid receptor CB1(CB1R). Thalamic and cortical synapses also compete for the availability of PRPs. The stimulation of an additional thalamic

projection leads to an unbalance between the number of activated synapses and PRPs availability, leading to competition. Synaptic competition is also modulated by time: extending the time window of the second thalamic stimulation to 30 minutes, decreases synaptic competition. As for cooperation, CB1R activation also restricts synaptic competition. Since CB1R activation is involved in discriminative learning, it is conceivable that by limiting cortical-to-thalamic cooperation, the endocannabinoid signalling limits generalisation. Our results show that cortical and thalamic inputs to the LA can cooperate and compete within large time windows, allowing a continuous integration of information at amygdala synapses.

Disclosures: **N. Madeira:** None. **R. Fonseca:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.02/D62

Topic: B.08. Synaptic Plasticity

Support: China NSF Grant 31271155

Title: Long-term synaptic plasticity of EPSPs in different pathways of spinal cord motoneurons *In vitro*

Authors: ***M.-Y. WANG**[1], Y.-Y. SU[2], X. JIANG[2], J.-H. JIN[2], H. LUO[2], H. SONG[2], L. ZHANG[2], Y.-H. SHI[2], Y.-L. WANG[2], B.-A. WANG[1]
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Abstract: To explore the possible synaptic plasticity mechanisms as a candidate of neural basis underlying the ability of motor learning in spinal cord motoneurons (MNs), the intracellular recordings were performed from MNs in neonatal rat spinal cord slices and excitatory postsynaptic potentials (EPSPs) were evoked by ipsilateral dorsal root (iDR), ipsilateral and contralateral ventrolateral funiculus (iVLF and cVLF), and ipsilateral pericentral canal (iPCC) stimulation, *i.e.* iDR-, iVLF-, cVLF- and iPCC-EPSPs, respectively. After tetanic stimulation, the increase in EPSP amplitude to more than 120% of control level and at least for 30 min could be referred to as long-term potentiation (LTP). After tetanic stimulation on iDR in 26 MNs, LTP of iDR-EPSPs (*i.e.* iDR-LTP) was observed in 17 cells, usually with the increase of area under curve, the prolonging of duration and so on. Similarly, the tetanic stimulation on iVLF, cVLF and iPCC also induced LTP of iVLF-EPSP (iVLF-LTP) in 11 cells of 27 tested MNs, of cVLF-EPSP (cVLF-LTP) in 2 MNs, and of iPCC-EPSP (iPCC-LTP) in 11 cells of 33 tested MNs, respectively. Among 9 tested MNs with iVLF-LTP, the paired-pulse facilitation ratios of amplitude of iVLF-EPSPs elicited by paired-pulse stimulation were different from the baseline in

7 MNs. The analyses of apparent receptor kinetics of iVLF- or iPCC-EPSPs during iVLF- in 5 MNs or iPCC-LTP in 11 MNs showed that apparent dissociation rate constant (K_2) and apparent equilibrium dissociation constant (K_T) decreased in 3 or 5 MNs, respectively. These data suggest that there may be some forms of LTP in excitatory synaptic transmission in different pathways of MNs in the spinal cord, and it could be considered as a candidate of neural basis underlying the ability of motor learning.

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Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.03/D63

Topic: B.08. Synaptic Plasticity

Support: MC_U105174197

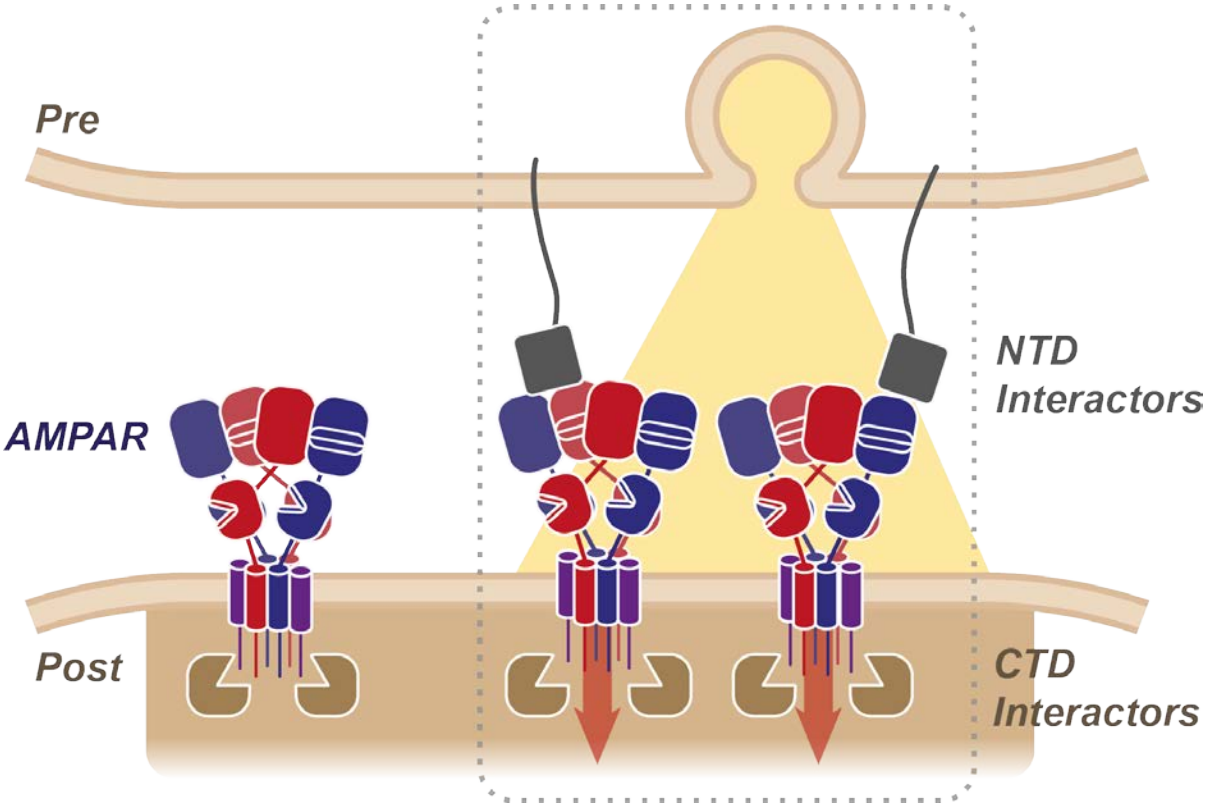
Title: Molecular mechanisms controlling AMPA receptor anchoring in synaptic transmission and plasticity

Authors: *J. F. WATSON, H. HO, I. H. GREGER
MRC Lab. of Mol. Biol., Cambridge, United Kingdom

Abstract: AMPA-type glutamate receptors (AMPARs) are embedded at the postsynapse, aligned with the presynaptic neurotransmitter release machinery, mediating fast excitatory neurotransmission [1]. A prerequisite for faithful signal transmission is AMPAR trapping and clustering at postsynaptic sites [2]. Synapse strengthening, as occurs during learning, results from the recruitment to and enrichment of AMPARs at synapses. Therefore, the core mechanisms for AMPAR positioning are fundamental to synaptic transmission and plasticity. AMPAR synaptic anchoring has historically been attributed to C-terminal (CTD) interactions with components of the postsynaptic scaffold, yet this model has been challenged [3]. We have recently shown that the AMPAR N-terminal domain (NTD), which projects midway into the synaptic cleft, plays a critical role in this process [4]. This highly sequence-diverse domain mediates synaptic anchoring in a subunit-selective manner. Using a combination of electrophysiological and imaging techniques we have revealed that receptors lacking the NTD are unable to maintain faithful synaptic transmission, and despite being robustly expressed at extra-synaptic sites, are unable to sustain long-term potentiation (LTP).
To understand the essential requirements for subunit-specific AMPAR synaptic anchoring, we use paired synaptic recordings from single-cell electroporated neurons expressing AMPARs with targeted mutations to disrupt specific protein interactions. We demonstrate that AMPAR

anchoring in basal transmission and LTP is dependent on an interplay of multiple interactions mediated by the NTD, CTD and auxiliary subunits, which act as an ensemble to tune the postsynaptic response (see figure). By appreciating the precise contributions of each of these interactions to AMPAR synaptic anchoring we can progress towards fully understanding the regulation of receptor trafficking, which underlies synaptic transmission and plasticity.

[1] Greger et al. Neuron 2017
[2] MacGillavry et al. Neuron 2013
[3] Granger et al. Nature 2013
[4] Watson et al. Elife 2017



Disclosures: **J.F. Watson:** None. **H. Ho:** None. **I.H. Greger:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

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Topic: B.08. Synaptic Plasticity

Support: the Research Grants Council of Hong Kong SAR (C6003-14G)

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Title: IL-33 enhances the development of hippocampal excitatory synapses

Authors: K.-W. HUNG[1,2,3,4], Y. WANG[1,2,3,4], F. CHUANG[1,2,3,4], A. FU[1,2,3,4], *W.-Y. FU[1,2,3,4], N. IP[1,2,3,4]
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Abstract: Emerging evidence suggests that immune proteins not only maintain body homeostasis, but also possess non-immune functions during physiological development. Interleukin (IL)-33, originally identified as an alarmin, acts as a crucial mediator that initiates and amplifies innate immune responses during tissue injury. Our laboratory previously demonstrated that IL-33 treatment ameliorates the deficits of synaptic plasticity and cognitive impairment, and reduces Alzheimer's disease-like pathology in APP/PS1 mice, a transgenic mouse model of the disease. In the present study, we show that IL-33 plays critical roles in synaptic development and functions in the hippocampus. IL-33 treatment increased the number of dendritic spines in cultured hippocampal pyramidal neurons. Furthermore, IL-33 stimulated an increase in the number of excitatory synapses in hippocampal neurons, as indicated by increased co-localization of the presynaptic marker vGluT1 and postsynaptic marker PSD-95. Functionally, IL-33 treatment increased the frequency of miniature excitatory postsynaptic currents in cultured hippocampal neurons, suggesting enhanced spontaneous neurotransmission. These findings demonstrate a novel role of IL-33 in excitatory synapse development and functions in the hippocampus.

Disclosures: K. Hung: None. **Y. Wang:** None. **F. Chuang:** None. **A. Fu:** None. **W. Fu:** None. **N. Ip:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

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Program#/Poster#: 040.05/E2

Topic: B.08. Synaptic Plasticity

Support: JSPS KAKENHI 15H04258

a research fund from Shionogi & CO., LTD

Title: Roles of Arc/arg3.1 on surface expression dynamics of AMPA receptors during structural plasticity and on cognitive refinement processes

Authors: *H. OKUNO[1], Y. ISHII[2], T. ENDO[2], M. UEHARA[1], Y. SUZUKI[1], K. MINATOHARA[1], A. ARAKI[1], M. ABE[3], I. IMAYOSHI[1], M. KAKEYAMA[4], K. SAKIMURA[3], H. BITO[2]
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Abstract: The neuronal immediate early gene *Arc* plays critical roles in synaptic plasticity and homeostatic scaling by regulating AMPA receptor (AMPA-R) trafficking. We previously proposed the inverse synaptic tagging mechanism of *Arc* for synapse-specific AMPA-R regulation (Okuno et al., Cell, 2012). However, the exact AMPA-R dynamics associated with *Arc*-mediated inverse tagging remains unknown. To address this issue, we developed a live imaging system that enabled to record subunit-specific AMPA-R lateral diffusion during structural plasticity in *Arc*-knockout (*Arc*-KO) and wildtype (WT) hippocampal neurons. We found that long-term potentiation (LTP) of surface GluA1/GluA2 levels in spines with volume expansion was undistinguishable between WT and *Arc*-KO neurons. However, in consistent with the inverse tagging of *Arc* to weak synapses, surface GluA1/GluA2 complex gradually decreased in non-expanding spines of WT neurons during the late phase of structural plasticity, and this effect was abolished in *Arc*-KO neurons. In contrast, LTP of surface GluA2/GluA3 levels showed a significant increase in *Arc*-KO neurons in expanded spines immediately after structural plasticity, while no effect was observed on non-expanded spines. Thus, disruption of *Arc* orthogonally affected distinct of AMPA-R compositions during early and late phases of LTP in potentiated and non-potentiated spines, without affecting plasticity induction and expression *per se*. These findings strikingly correlated with the normal acquisition yet dysfunctional behavioral refinement in *Arc*-KO mice in two independent target-switching tasks. Network analysis of behavior during the task demonstrated a deficit in target precision in *Arc*-KO mice. Taken together, our findings suggest a novel synaptic mechanism by which *Arc* expression regulates cognitive refinement processes such as memory precision and behavioral flexibility.

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None. **M. Abe:** None. **I. Imayoshi:** 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.; Shionogi & CO., LTD. **M. Kakeyama:** None. **K. Sakimura:** None. **H. Bito:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.06/E3

Topic: B.08. Synaptic Plasticity

Support: KY Sci. and Eng. FDN, KSEF-3712- RDE-019

University of KY Office of Undergraduate Research

Deutscher Akademischer Austausch Dienst (DAAD) German Academic Exchange Service. RISE

Title: Retrograde signaling depends on electrical activity of target tissue

Authors: *J. MCCALL[1], M. MATTINGLY[1], C. HERMANNS[1], C. BALLINGER BOONE[1], T. DONOVAN[1], B. SLABACH[1], K. WEINECK[1,2], M. MELODY[1], N. D[1], E. SOMASUNDARAM[1], C. MALLOY[1], R. COOPER[1]
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Abstract: Synapse formation and maintenance involves a two way communication to and from the target. The neuromuscular junction (NMJ) continues to be a model in addressing the development and homeostatic regulation in synaptic interaction. We are addressing prolonged electrical inhibition and excitation of the synaptic target throughout development to determine if increased or decreased electrical activity influences nerve terminal formation. With the use of optogenetics, in the larval Drosophila model, expressing light sensitive proteins (Channel rhodopsins & halorhodopsin) specifically in muscle, the electrical activity of the synaptic target is controlled in various conditioning paradigms. Results are preliminary at this time. We hypothesis that inhibition of the muscle in a dose -dependent manner will result in the motor nerve terminal growth to correlate with the activity by enhancing growth with less muscle activity and retarding growth with increased target activity. This study is significant as a better understanding in the repetitive and long term use of the light sensitive channels obtained as well as the influence of inhibition and excitation of target tissues on the retrograde impact on developing synapses. In addition, the impact by decreasing muscle activity by disease states or weightlessness on NMJ structure and function is addressed in this physiological model system.

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Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.07/E4

Topic: B.08. Synaptic Plasticity

Support: XDB02050002

Title: Structure and plasticity of silent synapses in developing hippocampal neurons visualized quantitatively by super-resolution imaging

Authors: *C. XU[1,2], H. LIU[2], L. QI[2], G. HAO[3], Z. SHEN[2], Y. WANG[2], H. BABCOCK[3], P.-M. LAU[2], X. ZHUANG[3], G. BI[2]
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Abstract: Excitatory synapses in the mammalian brain exhibit diverse functional properties in transmission and plasticity. Directly visualizing the structural correlates of such functional heterogeneity is often hindered by the diffraction-limited resolution of conventional optical imaging techniques. In this work, we used super-resolution stochastic optical reconstruction microscopy (STORM) to resolve structurally distinct excitatory synapses formed on dendritic shafts and spines. The majority of shaft synapses contained N-methyl-D-aspartate receptors (NMDARs), but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), indicated that they were functionally silent. During development, as more spine synapses formed and grew with increasing AMPAR and NMDAR expression, the density of silent shaft synapses remained largely constant, with similar NMDAR levels. Upon induction of chemical long-term potentiation (cLTP) by glycine stimulation and quantitative analysis, the previously silent shaft synapses recruited more AMPARs than did spine synapses. Thus, silent shaft synapse as a special synaptic state may serve as a "reserved" pool to be functionalized through activity-dependent plasticity.

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Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant NS097498

Title: Actions of Rab27B-GTPase on central excitatory synaptic transmission

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Abstract: Streaming of information throughout the nervous system is determined by the ability of individual neurons to convey information from one to another through arrays of discrete synaptic connections. Each synapse is comprised of tightly apposed pre- and post-synaptic compartments and, for the presynaptic compartment, complexes of proteins target synaptic vesicles (SV) to the active zone and direct exocytotic and endocytotic activity. Rab-GTPase proteins have long been proposed to serve as key regulators of SV cycling. Indeed, it has been shown that deficiency of Rab3a reduces evoked neurotransmitter (NT) exocytosis in cultured hippocampal neurons (CHN) and completely attenuates LTP at MF-CA3 synapses in hippocampal slices (HS). Yet KO of all four isoforms of Rab3 only demonstrated a 30% decrease in evoked synaptic transmission in CHN. Rab27B, is a highly homologous Rab-GTPase that also localizes to SV, although its functional role in spontaneous and evoked synaptic physiology is largely unknown. Our general hypothesis is that Rab3 isoforms and Rab27B exert distinct actions but also can exhibit a high degree of functional overlap. Here we examined the effect of Rab27B KO on spontaneous NT release in CHN, as well as on evoked synaptic transmission and synaptic plasticity in HS. IHC of Rab27B in HS from wild-type (WT) mice confirmed that Rab27B is highly expressed in the mouse hippocampus and that expression was lost in the KO. The KO of Rab27B did not significantly alter the levels of expression of Rab3a nor several other presynaptic proteins. fEPSP recordings at the SC-CA1 synapse showed that there is a slight increase in the slope of the fEPSP input-output (I-O) relationships of KO mice in response to SC field stimulation compared to controls. Comparison of the slope of the fEPSP as a function of the fiber volley amplitude indicated that the I-O relationship of KO mice is slightly shifted to the left compared to controls, suggesting that at a given presynaptic discharge the fEPSP is larger in KO mice. Evaluation of short-term synaptic plasticity by paired-pulse ratio (PPR) demonstrated that for ISI of less than 100 milliseconds PPR was decreased in KO mice compared to controls. Paradoxically, the strongest synaptic effect observed in the SC-CA1 region

of Rab27B KO mice was a significant attenuation of LTP relative to control, a site where Rab3A KO had no effect on LTP. In summary, Rab27B deficiency demonstrates a modest effect on PPR at the SC-CA1 synapse but a strong effect on LTP. This data indicates both pre- and post-synaptic roles, and based on prior reports Rab27B actions at SC-CA1 are strikingly different from that previously observed for the Rab3a KO mouse.

Disclosures: E.R. Arias Hervert: None. **M. Njus:** None. **G.G. Murphy:** None. **S. Lentz:** None. **S. Ernst:** None. **E.L. Stuenkel:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.09/E6

Topic: B.08. Synaptic Plasticity

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Kahlert Foundation

Title: The role and regulation of dendritic mitochondrial fission during long-term potentiation

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Abstract: Long-term potentiation (LTP) is the prevailing cellular mechanism of synaptic strengthening and is of immense importance to understanding synaptic physiology. Mitochondrial functions, such as glutamate synthesis, ATP synthesis, and calcium handling, are postulated to be especially important for synaptic transmission, and demands on these functions are likely to change during synaptic plasticity. Accordingly, there has been a recent boom in the study of neuronal mitochondria, and it has become apparent that synaptic transmission relies on the adequate presence and function of mitochondria. However, whereas the role of presynaptic mitochondria in presynaptic function has been extensively explored, the mechanisms underlying LTP predominantly occur postsynaptically. Motivated by this contrast, we tested whether dendritic mitochondrial morphology is impacted in the context of LTP. In dendrites of cultured rat hippocampal neurons at rest, mitochondria were stable and rarely underwent fission or fusion. However, we found that a protocol to chemically induce LTP (cLTP), prompted a large and transient burst of dendritic mitochondrial fission. This burst of fission was dependent on

NMDAR activation. Mitochondrial fission canonically involves actin nucleation and membrane constriction by the GTPase dynamin-related protein 1 (Drp1). Consistent with this mechanism, inhibition of actin polymerization suppressed the fission burst, and expression of a dominant negative mutant of Drp1 completely prevented cLTP-induced fission of dendritic mitochondria. Furthermore, dominant negative Drp1 also prevented the increase in spine size and surface synaptic AMPARs following cLTP stimulation. Drp1 itself is regulated by phosphorylation and, intriguingly, signaling molecules activated by NMDARs during LTP induction such as CaMKII, CaMKIα, and calcineurin are known in other cells to regulate Drp1-dependent fission, suggesting a direct mechanism whereby NMDAR activation could impact mitochondrial structure and dynamics. Taken together, these data suggest that NMDAR-dependent LTP induction increases dendritic mitochondrial fission, which contributes to LTP expression. Impaired synaptic function is implicated in myriad neuropsychiatric diseases, many of which are also associated with mitochondrial dysfunction. This raises the important question of whether neuronal mitochondrial dysfunction contributes to synaptic and cognitive impairment by perturbing synaptic plasticity.

Disclosures: S. Divakaruni: None. **M. Contreras:** None. **H.N. Higgs:** None. **T.A. Blanpied:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.10/E7

Topic: B.08. Synaptic Plasticity

Support: VA BX003671

NIH NS073653

Title: Neuron-targeted caveolin-1 promotes ultrastructural and functional hippocampal synaptic plasticity

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Abstract: A delicate inter-neuronal communication between pre- and post-synaptic membranes is critical for synaptic plasticity and the formation of memory. Evidence shows that membrane/lipid rafts (MLRs), plasma membrane microdomains enriched in cholesterol and sphingolipids, organize presynaptic proteins and postsynaptic receptors necessary for synaptic

formation and signaling. MLRs establish a cell polarity that facilitates transduction of extracellular cues to the intracellular environment. Here we show that neuron-targeted overexpression of a MLR protein, caveolin-1 (*SynCav1*), in the adult mouse hippocampus increased number pre-synaptic vesicles (PSVs) per bouton, total excitatory type I glutamatergic synapses, number of same-dendrite multiple-synapse boutons (sdMSBs), increased myelination, increased LTP, and increased MLR-localized GluN receptor subunits. *In vitro* experiments using differentiated human neuronal progenitor cells (NPCs) derived from induced pluripotent stem cells (iPSCs), show that *SynCav1* increased dendritic arborization and axonal growth (as indicated by MAP2 and SMI 31 expression respectively), increased MLR formation and MLR-localization of Cav-1 and synaptic markers such as syntaxin-1a, synaptophysin, phosphorylated (P)-synapsin and P-CaMKII *in vitro*. Immunoprecipitation (IP) of MLR fractions from *SynCav1*-infected NPCs using a Cav-1 antibody revealed that Cav-1 IPed P-synapsin, but not synaptophysin, syntaxin-1a or P-CaMKII. In contrast, NPCs infected with a Cav-1 mutant that lacks the tyrosine 14 phosphorylation site (SynCav1(Y14A)) exhibited stunted axonal and dendritic growth, decreased expression of P-Src and P-Cav-1, and prevented MLR-localization of synaptic markers. These findings, which are consistent with a significant increase in ultrastructural and functional synaptic plasticity, provide a fundamental framework that underlies the previously demonstrated improvements in learning and memory in adult and aged mice by *SynCav1*. Such observations suggest that P-Cav-1 and MLRs alter basic aspects of synapse biology that could serve as potential therapeutic targets to promote neuroplasticity and combat neurodegeneration in a number of neurological disorders.

Disclosures: B.P. Head: None. **J. Egawa:** None. **S. Wang:** None. **A.M. Kleschevnikov:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

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Program#/Poster#: 040.11/E8

Topic: B.08. Synaptic Plasticity

Support: DA011289

T32 NS 62443-8

Title: Novel LTP at an opioid-sensitive GABAergic synapse in the VTA

Authors: *R. ST. LAURENT[1], J. A. KAUER[2,1]
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Abstract: Persistent opioid-induced changes in the reward pathway, such as the dopamine-rich ventral tegmental area (VTA), may precede the transition to addiction. Opioids decrease inhibition onto VTA dopamine cells leading to increased excitability. Spontaneous activity of dopamine cells in the VTA is tightly regulated by inhibitory inputs, and morphine exposure has been demonstrated to affect synaptic plasticity at inhibitory synapses. However, the VTA is a heterogeneous region with different subsets of neurons having different functional implications on behavior, and therefore, opioid-induced adaptations may also be heterogeneous. Recently, we discovered a novel form of long-term potentiation at opioid-sensitive inhibitory synapses in the VTA using a low frequency stimulation (LFS) pairing protocol (LFS-LTP_{GABA}). We observed LFS-LTP_{GABA} in dopamine cells recorded in the lateral VTA (LTP in 17/33 I_h^+ cells; LTP in 3/10 I_h^- cells) when IPSCs were evoked by electrically stimulating caudal to the VTA in a horizontal midbrain slice. The location of the stimulating electrode differs from other reports examining inhibitory synaptic plasticity in the VTA, including one finding that IPSCs exhibit LTD with LFS. These differences can most likely be attributed to stimulating different inputs onto dopamine cells. Using optogenetics, we are currently investigating possible input regions located caudal to the VTA that have GABAergic projections, including the rostromedial tegmental nucleus and the dorsal raphe. LFS-LTP_{GABA} may also occur in VTA dopamine cells projecting to particular output regions and our preliminary data suggests that dopamine cells projecting to the nucleus accumbens exhibit LTP. In addition to looking for circuit specificity, we analyzed the locus of plasticity and other interesting characteristics of these inputs. The LTP was accompanied by a decrease in paired pulse ratio, suggesting an increase in presynaptic release probability. Preliminary experiments in the presence of an NMDA receptor antagonist show that this LTP may be NMDAR-independent (LTP in 3/4 I_h^+ cells in the presence of d-AP5; IPSC amplitude normalized to baseline = 154±37%, n = 3 cells). Some of the potentiating inputs are unusually large and therefore may exert significant influence on the firing rate of dopamine cells. These unusually large inputs often exhibited LFS-LTP_{GABA} and were strongly depressed by opioid receptor activation with DAMGO (LTP in 5/7 cells). Our findings are the first to document opioid-sensitive inhibitory inputs onto VTA dopamine cells that potentiate with LFS.
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Disclosures: **R. St. Laurent:** None. **J.A. Kauer:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

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Topic: B.08. Synaptic Plasticity

Support: Deutsche Forschungsgemeinschaft (FOR 2419: FR 620/14-1)

Landesforschungsförderung Hamburg (LFF-FV27b)

M.F. is Research Professor for Neuroscience of the Hertie Foundation.

Title: Single mossy fiber synapses control hilar mossy cell firing owing to their previous activity

Authors: *A. DRAKEW, U. MAIER, M. FROTSCHER
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Abstract: The granule cells (GCs) of the dentate gyrus convey information from the entorhinal cortex to the hippocampus via their mossy fiber (MF) axons that establish giant synapses with CA3 pyramidal cells and hilar mossy cells (MCs). MCs project back to GCs directly and indirectly via interneurons thereby modulating entorhino-hippocampal information transfer. In order to understand how sparsely firing GCs control the high spike activity of MCs, we analyzed the impact of single MF synapses on MC activity in organotypic entorhino-hippocampal slice cultures. We combined single-bouton stimulation, whole-cell patch-clamp recording of MCs, and two-photon Ca^{2+} imaging of spines postsynaptic to the stimulated MF bouton. Patch pipettes contained Alexa 594 dextran and Fluo-4FF to visualize MC morphology and Ca^{2+} transients in single spines, respectively. Targeted patching of MF boutons presynaptic to labeled spines was facilitated by transient staining of the extracellular space with Alexa 488 hydrazide released from a second pipette (“Shadow patching”, Kitamura et al. 2008). Stimulation of MF boutons in loose-seal cell-attached mode evoked heterogeneous excitatory synaptic responses - even if two MF synapses located on the same MC dendrite were studied. We observed synapses eliciting suprathreshold excitatory postsynaptic potentials, directly detonating the target MC. This direct MC activation would reach numerous target granule cells and interneurons. Other MF synapses on MCs were subthreshold or gave rise to mixed sub- and suprathreshold responses. These different states of individual synapses were modified individually by the induction of plasticity. Thus, the outcome of plasticity induction depended on the initially encountered synaptic state, suggesting that a given synaptic state represents encoded previous activity at this synapse. In summary, individual GCs control MC firing by single strong but metastable synapses that are continuously modified by their use.

Disclosures: **A. Drakew:** None. **U. Maier:** None. **M. Frotscher:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 040.13/E10

Topic: B.08. Synaptic Plasticity

Support: Wellcome-DBT India Alliance Grant IA/I/12/1/500529 (S Nadkarni)

Title: Internal calcium stores and calcium regulation in CA1 spines

Authors: *G. MAHAJAN, S. NADKARNI
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Abstract: A transient rise in calcium at the post-synaptic locus is necessary for inducing long-lasting changes in synaptic efficacy. Models of activity-dependent plasticity (LTP/STDP) have traditionally attempted to link the direction and magnitude of synaptic changes to the properties of the Ca2+ time course (calcium control hypothesis). In these models, NMDA-R and voltage-gated (VGCC) channels on the plasma membrane provide the only sources of Ca2+ entry into the cell. However, intracellular stores in the endoplasmic reticulum (ER), which is present in dendritic processes, can also potentially contribute to shaping the Ca2+ signal in the post-synaptic spine. Several lines of experimental support in fact exist for an involvement of ER stores in Ca2+ handling at active spines and its downstream effects on plasticity. These span hippocampal LTP, STDP, structural and heterosynaptic plasticity, plasticity of spine VGCCs, and mGluR-mediated depression in diverse types of central neurons. EM studies have shown ER being present in individual spines as well as dendrites, and its extent could vary dynamically in response to Ca2+ fluctuations. Yet, despite considerable experimental work, there is still lack of clarity on the factors that govern the extent and distribution of ER in spines, and not much effort has been expended on the theoretical front to understand exactly what novel/additional properties the presence of ER stores confers on synapses. We have therefore taken up a computational approach to explore the role of ER in modulating calcium dynamics at the post-synaptic locus. Using biologically realistic models of a CA1 spine, we consider ER calcium release via Ryanodine receptor and IP3 receptor-gated channels, addressing the question of how the temporal properties of synaptic stimulation determine the differential recruitment of these two modes of calcium-induced calcium release (CICR) and their involvement in inducing plasticity. Besides directly contributing to Ca2+ signals, we also consider an additional modulatory role for ER Ca2+ release in indirectly tempering NMDA-R activation by decreasing membrane excitability. The balance between these contrasting effects of CICR may contribute to tuning the plasticity of the synapse, and may help to better understand multiple experimental findings surrounding ER stores, such as their role in STDP, the association of ER with potentiated mushroom spines, and impaired plasticity arising from some AD-linked mutations that result in aberrant CICR.

Disclosures: **G. Mahajan:** None. **S. Nadkarni:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

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Program#/Poster#: 040.14/E11

Topic: B.08. Synaptic Plasticity

Title: Cell firing bidirectionally regulates future long-term potentiation depending on the induction protocol

Authors: *R. U. HEGEMANN[1,2,3], W. C. ABRAHAM[1,2,3]
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Abstract: Distinct patterns of action potential (AP) firing are known to drive synaptic plasticity phenomena such as long-term potentiation (LTP). However, the role of cell firing in the regulation of future plasticity, i.e. metaplasticity, remains poorly understood. Some studies suggest that postsynaptic firing alone facilitates subsequent LTP induction, while others have shown cell firing to inhibit later LTP. With the aim of unravelling this inconsistency, we conducted single cell sharp-electrode recordings from CA1 pyramidal cells in acute hippocampal slices from 6-8 week old male Sprague-Dawley rats. Pyramidal cells were primed with depolarising current injections (1.4nA/2ms) into the soma to induce APs. Priming cells with either 3 sets of 3xTBS trains or 2 sets of 3x100 Hz (HFS) trains of APs significantly impaired Schaffer collateral LTP induced 15 min later with 1 train of synaptically driven TBS (control (n=7): 100.4 ± 16 %; 3x3 TBS primed (n=6): 39.9 ± 16.7 %, p=.02; 2x3 100 Hz primed (n=6): 31.9 ± 23.2 %, p=.04), measured 30 min post-induction. Because different LTP induction paradigms can activate distinct signalling pathways, we tested the hypothesis that the direction of the priming effect is dependent on the nature of the LTP induction protocol. Supporting this hypothesis, we found that LTP induced by HFS (2x100 Hz trains) was not affected by TBS priming while HFS priming facilitated this type of LTP, compared to control cells (control (n=10): 33 ± 8.8 %; 3x3 TBS primed (n=6): 32 ± 9.8 %; 2x3 100 Hz primed (n=8): 73.1 ± 14.3 %, p =.03)). Interestingly, primed cells fired fewer APs during LTP induction than control cells. While this was the case for both types of LTP induction, AP firing was only able to predict the amount of LTP induced by TBS but not by HFS. Taken together, our findings suggest that cell firing affects intracellular signalling pathways which downregulate cell firing but differentially affect LTP induction, depending on the specific mechanisms engaged by the induction protocols. There is also evidence that distinct patterns of cell firing might have diverse effects on LTP induced with HFS.

Disclosures: R.U. Hegemann: None. **W.C. Abraham:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant R01MH081060

NIH Grant R01MH070727

Title: Dissociating pre and postsynaptic functions of BDNF and TrkB signaling in synaptic plasticity

Authors: *P.-Y. LIN, E. KAVALALI, L. MONTEGGIA
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Abstract: BDNF is a signal integrator and modulator of synaptic plasticity, such as long-term potentiation (LTP), which is considered an electrophysiological correlate of learning and memory. BDNF increases presynaptic neurotransmitter release and enhances postsynaptic neurotransmitter sensitivity to induce synaptic plasticity by binding to its high affinity receptor, tyrosine receptor kinase B (TrkB), which is localized to both pre-and postsynaptic sites. BDNF/TrkB signaling facilitates LTP and is involved in learning and memory. However, the question of whether BDNF is released from pre-or postsynaptic site, and whether synaptic changes underlying LTP are mediated by pre- or postsynaptic TrkB downstream signaling remain elusive. To examine the exact location of BDNF release and to identify the role of presynaptic and postsynaptic TrkB during LTP induction, we injected a virus expressing Cre recombinase tagged to GFP (AAV-GFP-Cre) into either the CA3 (presynaptic neurons) or the CA1 (postsynaptic neurons) hippocampal regions of floxed BDNF mice or floxed TrkB mice. In this way, we could specifically delete BDNF or TrkB in these subregions of the hippocampus. We found that deletion of BDNF from CA3 attenuated but did not eliminate High Frequency Stimulation (HFS)-induced LTP; however, deletion of BDNF from CA1 blocked HFS-induced LTP. Moreover, deletion of TrkB from CA3 gradually reduced HFS-induced LTP suggesting that TrkB may regulate presynaptic release probability. The deletion of TrkB from CA1 nearly prevented HFS-induced LTP formation. Further experiments are underway to determine how presynaptic TrkB mediates release probability, and how pre-or postsynaptic BDNF and TrkB engages in different type of synaptic plasticity.

Disclosures: P. Lin: None. **E. Kavalali:** None. **L. Monteggia:** None.

Poster

040. LTP: Pre- and Postsynaptic Mechanisms I

Location: Halls A-C

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Program#/Poster#: 040.16/F1

Topic: B.08. Synaptic Plasticity

Support: Deutsche Forschungsgemeinschaft, Forschungsstipendium

Title: The role of neuroligin 1 in LTP

Authors: *X. WU[1,2], A. M. RILEY[2,1], T. C. SUDHOF[2], R. C. MALENKA[1]
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Abstract: Synaptic cell-adhesion molecules (CAMs) connect pre- and postsynaptic specializations at synapses and have been proposed to play multiple functional roles. Among the best characterized synaptic CAMs are presynaptic neurexins (NRXs) and postsynaptic neuroligins (NLs), which interact across the synaptic cleft. Neuroligins have four isoforms (1-4), with NL1 present at excitatory synapses. Previous work in our lab found that genetic deletion of NL1 inhibits NMDA receptor (NMDAR)-dependent LTP in CA1 pyramidal neurons of mice (Jiang et al., 2016). Here we perform a series of molecular replacement experiments to determine the detailed mechanisms underlying this phenotype. To address this question, we generated lentiviruses containing Cre recombinase and various mutant forms of NL1 and delivered them to CA1 pyramidal neurons *in vivo* into NL1 or NL1234 conditional knockout (cKO) mice (age 21 d). Two weeks later, we performed whole cell voltage clamp recordings from CA1 pyramidal neurons in standard acute slices. Standard NMDAR-dependent LTP (induced by giving 2, 100 Hz/ 1 sec tetani separated by 20 sec while holding cells as 0 mV) as well as LTP induced by activation of voltage-gated calcium channels (VCGGs) were both fully rescued by expression of wildtype NL1 (NL1WT) after cKO of NL1. Similarly, both NMDAR- and VGCC-dependent LTP were rescued by expression of the extracellular domain of NL1 alone in both NL1 and NL1234 cKO mice. This result demonstrates that the NL1 intracellular domain is dispensable for LTP. However, while NL1WT rescued the decrease in the NMDAR/AMPAR ratio of evoked EPSCs in the NL1234 cKO mice, expression of NL1 lacking its intracellular tail did not. This result provides a clear molecular dissociation between the role of NL1 in LTP and its role in maintaining a normal complement of synaptic NMDARs (as measured by evoked EPSCs). In addition, expression of NL1 with mutations in its extracellular NRX binding site did not rescue LTP in the NL1234 cKO while the NMDAR/AMPAR ratio was rescued. These results provide further support that the roles of NL1 in LTP and influencing synaptic NMDARs are molecularly dissociable.

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Poster

041. Long-Term Depression

Location: Halls A-C

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Topic: B.08. Synaptic Plasticity

Support: National INtitute of Neurological Diseases and Stroke Grant R15NS078645

National Institute of Drug Abuse Grant R15DA038092

Institutional Mentoring Environment Grant

Title: CB1-dependent LTD in ventral tegmental area GABA neurons: A novel target for marijuana

Authors: *I. OSTLUND[1], L. N. FRIEND[2], J. WEED[2], P. SANDOVAL[3], J. G. EDWARDS[2]
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Abstract: The ventral tegmental area is necessary for reward behavior where dopamine cells are critical for reward motivated behavior and attaching salience to novel rewarding stimuli. These dopamine cells are regulated by neighboring inhibitory GABA cells. Synaptic modifications known as synaptic plasticity are common in the VTA and thought to be tied to memory of reward and thus behavioral motivation. While dopamine cell plasticity has been thoroughly examined, much less is known regarding GABA cell plasticity. Using whole cell electrophysiology in juvenile/adolescent GAD67-GFP knock-in mice we examined excitatory plasticity in fluorescent VTA GABA neurons. A novel long-term depression (LTD) was induced in GABA cells that was dependent on cannabinoid receptor 1 (CB1) and metabotropic glutamate receptor 5. LTD was absent in CB1 knock-out mice, but preserved in heterozygous littermates. Chronic injections of Δ^9-tetrahydrocannabinol (THC), a psychoactive ingredient in marijuana, occluded LTD compared to vehicle injections, however, a single exposure was insufficient to occlude LTD. Bath application of THC induced depression of glutamate synaptic activity and therefore downstream dopamine cells could be disinhibited, which would potentially result in increased reward. As synaptic modifications by drugs of abuse are often tied to addiction, this data also suggests a possible mechanism for the addictive effects of THC, which is most commonly seen in adolescents, by potentially altering reward behavioral outcomes.

Disclosures: I. Ostlund: None. **L.N. Friend:** None. **J. Weed:** None. **P. Sandoval:** None. **J.G. Edwards:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

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Program#/Poster#: 041.02/F3

Topic: B.08. Synaptic Plasticity

Title: Paired-associative quadripulse stimulation (PA-QPS) - alterations of QPS effects by electrical stimulation on peripheral nerve

Authors: *W. WIRATMAN[1,3], T. MURAKAMI[2], S. KOBAYASHI[2], H. ENOMOTO[2], Y. UGAWA[2]

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Abstract: Background: Repeated bursts of four monophasic TMS pulses (QPS) is known to induce long-term potentiation/depression (LTP/LTD)-like synaptic plasticity. Short interstimulus-interval (ISI) of 5ms increases corticospinal excitability, while QPS at long ISI of 50ms decreases it. Paired-associative stimulation (PAS), repeated TMS of M1 pairing with peripheral electrical nerve stimulation (ES), also leads to bidirectional synaptic plasticity. The magnitude and directions of induced plasticity are dependent on interpair-intervals (IPIs): IPIs of N20+2ms/N20-5ms lead to enhancement/reduction of synaptic plasticity. Objective: We modified a QPS protocol by pairing bursts of four ES (paired-associative QPS, PA-QPS) and investigated how PA-QPS modulates the corticospinal excitability. Methods: Eighteen healthy subjects participated in this study. We delivered QPS (QPS_{LTP} or QPS_{LTD}) to the left M1 and PA (PA_{LTP} or PA_{LTD}) at the right median nerve. We tested six different protocols (QPS_{LTP} only, QPS_{LTD} only, PA_{LTP}-QPS_{LTP}, PA_{LTD}-QPS_{LTP}, PA_{LTP}-QPS_{LTD}, and PA_{LTD}-QPS_{LTD}) for each subject. When PA was combined with QPS, ES was given with asynchrony to TMS by -5ms or 2ms delay (N20-5ms / N20+2ms). The ISI of QPS was set at 5ms or 50ms and delivered every 5s for 30 min. For PA-QPS protocols, there were 360 pairs of ES - QPS bursts (total 1440 TMS and 1440 ES). For evaluating corticospinal excitability, single-pulse TMS was applied over the left M1 and motor evoked potentials (MEPs) were recorded from the right abductor pollicis brevis muscle before and after the interventions up to 60 min. Results: QPS_{LTP} increased and QPS_{LTD} decreased MEP. The depressive effect of QPS_{LTD} was enhanced by pairing PA_{LTD} and disappeared by pairing PA_{LTP}. The enhancement effect of QPS_{LTP} did not change significantly by pairing PA_{LTP}, but it showed depressive effect of QPS_{LTP} by pairing PA_{LTD}. Discussions: Enhancement and cancellation of LTD-like effect in PA-QPS_{LTD} protocols can be explained by additive effects of associative synaptic plasticity. Physiological processes of PA and QPS are distinct, thus $PA_{LTD/LTP}$ may accelerate or cancel out, respectively, the induction of LTD-like plasticity of QPS_{LTD}. However, PA-QPS_{LTP} protocols lacked the additive effects of associative plasticity. The narrower bursts of TMS-ES pairs might interfere the induction of associative plasticity.

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Poster

041. Long-Term Depression

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Topic: B.08. Synaptic Plasticity

Support: Millennium Nucleus NU-MIND NC-130011

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CONICYT 21140834

Title: Serotonin induces inhibitory synaptic plasticity in prefrontal cortex

Authors: *K. MORALES[1], *K. MORALES[1,2], P. R. MOYA[1,2,3], M. FUENZALIDA[1,2]
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Abstract: The prefrontal cortex (PFC) constitutes the highest level of the cortical hierarchy. PFC is a key brain structure involved in social and cognitive functions such as learning and memory, and where disruption of synaptic function is believed to contribute to several neuropsychiatric disorders. The GABAergic local system is especially important to fine-tuning of the excitatory-inhibitory balance required to enable proper integration of afferent information and sustain optimal computational capacity in the PFC. Several lines of evidence indicate that the complex action of serotonin (5-HT) in inhibitory synaptic function is determined by distinct 5-HT receptor (5-HTR) subtypes. However, the relative contribution of each receptor subtype to the regulation of inhibitory synaptic efficacy and plasticity remains still elusive. Through electrophysiological patch-clamp recordings, we studied the changes in the inhibitory synaptic plasticity generated by activation of 5-HTRs. The acute application of 5-HT (50 μM) induces long-lasting modifications in evoked inhibitory post-synaptic current (eIPSC) in PFC pyramidal neurons of Layer 2/3 from synaptic inputs of Layer 2/3 and Layer 5 interneurons. Depending on the 5-HTR subtype, 5-HT induces either long-term depression (LTD) or long-term potentiation (LTP) of GABAergic transmission. The induction of LTD requires the activation of 5-HT2a/5-HT3a receptors, whereas LTP requires activation of 5-HT1a receptors. Our results suggest that both form of synaptic plasticity LTP or LTD may depend on the identity in GABAergic inputs. Thus, our results suggest that 5-HT-dependent changes in the GABAergic efficacy of PFC could be an important functional target for the treatment of different neuropsychiatric diseases such as anxiety, obsessive-compulsive disorder and schizophrenia.

Disclosures: K. Morales: None. **P.R. Moya:** None. **M. Fuenzalida:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.04/F5

Topic: B.08. Synaptic Plasticity

Support: ZIA AA 000407

Title: D2 receptors on D2 MSNs and cholinergic interneurons modulate striatal endocannabinoid dependent long-term synaptic depression

Authors: *S. M. AUGUSTIN, D. LOVINGER
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Abstract: The dorsal striatum (DS) integrates information from cortex, thalamus, and midbrain inputs that form synapses on striatopallidal and striatonigral medium spiny neurons (MSNs). Changes in synaptic transmission at these synapses contribute to action control and learning by adjusting the gain on incoming signals. The best understood form of striatal synaptic plasticity is endocannabinoid (eCB) mediated long-term depression at corticostriatal glutmatergic synapses (LTD), which requires dopamine (DA) D2 receptors (D2Rs). These receptors are expressed on one of the two MSN populations, striatopallidal D2 receptor-expressing MSNs (D2 MSNs), and on cholinergic interneurons (Chls). Two different mechanisms for D2 involvement in LTD induction have been proposed; one involving the D2Rs on the D2 MSNs and the other involving the ChI D2Rs. However, pharmacological methods cannot distinguish D2R effects in a neuron-specific manner. Mice carrying a “floxed” D2 allele were bred with mice expressing the Cre recombinase under the control of the D2 MSN-active A2A promoter or ChAT-IRES promoter to remove D2Rs from D2 MSNs or Chls, respectively, and high frequency stimulation (HFS)-induced eCB mediated LTD was examined. D2R modulation of DA transmission is similar in the D2 MSN knockout (KO) mice and D2 Chl KO mice compared to their controls, indicating that off-target effects, such as loss of D2 autoreceptors, do not occur in these KO mice. In field potential recordings, HFS induces an eCB dependent LTD of a similar magnitude in brain slices obtained from D2 MSN KO mice compared to controls. HFS did not induce LTD in brain slices obtained from mice that lack D2Rs on Chls. In whole cell-recordings, removing D2Rs from D2 MSNs impaired induction of LTD only at synapses onto the D2 MSNs, and not those on neighboring striatonigral MSNs that do not contain D2Rs. This loss is correlated with deficits in DS mediated behaviors. HFS did not induce LTD at synapses onto MSNs in the D2 Chl KO mice. Our data indicate that Chl D2Rs modulate the induction of HFS-LTD at MSN synapses, and D2Rs on D2 MSNs modulate LTD, but only on D2 MSNs.

Disclosures: S.M. Augustin: None. **D. Lovinger:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.05/F6

Topic: B.08. Synaptic Plasticity

Support: Association for Migraine Disorders (BP, HBS, JAK, DL)

Deutsche Forschungsgemeinschaft PR 1719/1-1 (BP)

NS088453 (JAK)

NS055251 (DL, JAK)

Title: Optogenetically driven LTD of nociceptive inputs to trigeminal nucleus; Implications for migraine

Authors: *B. PRADIER[1], *B. PRADIER[1], H. B. SHIN[1], D. LIPSCOMBE[2], J. A. KAUER[1]
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Abstract: Migraine is a disabling and episodic brain disorder with high prevalence and complex pathophysiology. Animal models suggest that sensitization of the trigeminovascular pathway plays a major role in the pathology of migraine, yet little is known about long-term changes in trigeminal afferents or their synapses in the brainstem trigeminal nucleus *pars caudalis* (TNC). We used mice expressing channelrhodopsin-YFP in TRPV1 lineage neurons (generated from TRPV1-Cre (B6.129-Trpv1tm1(cre)Bbm/J)) to investigate different forms of synaptic plasticity at nociceptive primary afferents projecting onto second order relay neurons within the TNC. Based on immuno-labeling in trigeminal ganglia, we found that TRPV1 lineage afferents mostly co-localized with peptidergic, CGRP-containing cells (38 ± 2%) and non-peptidergic, IB4-expressing neurons (32 ± 4%). Thus, optical stimulation of TNC slices should activate a specific subset of primary afferents that are predominantly nociceptors. In laminae I-II neurons of acutely prepared transverse TNC slices, optical stimulation at the dorsolateral slice edge (473 nm, 0.4 - 1 msec) evoked excitatory postsynaptic currents (EPSCs) that were often polysynaptic. Using low-frequency stimulation (LFS, 1 Hz), we induced a robust form of long-term depression (LTD) of optically-evoked EPSCs (64 ± 9 %, n = 17, p = 0.0014). LTD was prevented by pre-incubation of brainstem slices with the NMDA receptor antagonist APV. Next, we investigated the effect of triggers of human migraine, on optically-evoked EPSCs. We bath applied the neuropeptide pituitary adenylate cyclase-activating peptide (PACAP), the nitric oxide donors nitroglycerin (NTG), or sodium nitroprusside (SNP). All three compounds depressed optically-evoked EPSCs within 16 - 20 min of their application (PACAP: 70 ± 8%, n = 6, p = 0.019; NTG: 73 ± 8%, n = 8, p = 0.013; SNP: 70 ± 7%, n = 11, p = 0.017). Our data show that LTD at nociceptive afferent synapses is a robust form of NMDAR-dependent synaptic plasticity in the trigeminal nucleus caudalis. This form of plasticity also occurs following PACAP, NTG and SNP application suggesting that depression at these synapses might contribute to sensitization of the trigeminovascular pathway and thus to migraine.

Disclosures: B. Pradier: None. **H.B. Shin:** None. **D. Lipscombe:** None. **J.A. Kauer:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.06/F7

Topic: B.08. Synaptic Plasticity

Support: National Natural Science Foundation of China 31070931

Title: BDNF val66met polymorphism impairs hippocampal long-term depression by down-regulation of 5-HT3 receptors

Authors: *Y. HUANG[1], R. HAO[2], Y. QI[2], Y.-Y. JI[3], C.-Y. ZHENG[3], W.-H. YUNG[4], B. LU[5]
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Abstract: Brain-derived neurotrophic factor (BDNF) is a key regulator of neuronal plasticity and cognitive functions. BDNF val66met polymorphism, a human single-nucleotide polymorphism (SNP) in the pro-domain of BDNF gene, is associated with deficits in activity-dependent BDNF secretion and hippocampus-dependent memory. However, the underlying mechanism remains unclear. Here we show that in the $BDNF^{Met/Met}$ mouse line mimicking the human SNP, BDNF expression in the hippocampus was decreased. There was a reduction in the total number of cells in hippocampal CA1 region, while hippocampal expression of mRNAs for NR2a, 2b, GluR1, 2 and $GABA_AR\beta3$ subunits were up-regulated. Although basal glutamatergic neurotransmission was unaltered, hippocampal long-term depression (LTD) induced by low-frequency stimulation was impaired, which was partially rescued by exogenous application of BDNF. Interestingly, 5-HT3a receptors were down-regulated in the hippocampus of $BDNF^{Met/Met}$ mice, whereas 5-HT2c receptors were up-regulated. Moreover, impaired LTD in $BDNF^{Met/Met}$ mice was reversed by 5-HT3aR agonist. Thus, these observations indicated that BDNF val66met polymorphism changes hippocampal synaptic plasticity via down-regulation of 5-HT3a receptors, which may underlie cognition dysfunction of Met allele carriers.

Disclosures: **Y. Huang:** None. **R. Hao:** None. **Y. Qi:** None. **Y. Ji:** None. **C. Zheng:** None. **W. Yung:** None. **B. Lu:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.07/F8

Topic: B.08. Synaptic Plasticity

Support: Boston Children's Hospital Translational Research Program

Repository Core for Neurological Disorders, Department of Neurology, Boston Children's Hospital, and the IDDRC (NIH P30HD018655)

Title: Inhomogeneous modulation of cortical excitability by cathodal direct current stimulation in mouse and human cortex

Authors: *Y. SUN[1,2], S. C. DHAMNE[1,2], M. C. GOLDENBERG[1], J. R. MADSEN[3], A. ROTENBERG[1,2,4]
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Abstract: Objective: Cathodal transcranial direct current stimulation (DCS) is a method for focal noninvasive cortical stimulation, which leads to lasting depression in cortical excitability, resembling long-term depression (LTD), and dependent on mGluR5-mTOR pathway activation. Yet, whether the entirety of cortex exposed to cathodal DCS undergoes LTD-like change is unknown. We applied both in vitro cathodal DCS and in vivo cathodal transcranial DCS (tDCS) to test whether DCS-mediated changes in cortical excitability were uniform throughout the stimulated cortical volume. We also tested a novel drug-device pair aimed to facilitate a uniform cortical response to DCS. **Methods:** DCS was delivered through Ag/AgCl electrodes to isolated mouse primary motor cortical (M1) slices, to isolated human cortical slices derived from epilepsy surgery, or to the dorsal scalp of anesthetized mice. %change in field excitatory postsynaptic potential (fEPSP) slopes recorded by microelectrode array spanned across all cortical layers, 1 hour after isolated in vitro slice DCS, was plotted as an interpolated two-dimensional map. One hour after in vivo cathodal tDCS, M1 slices were isolated for phospho-S6 ribosomal protein (Ser240/244, pS6) immunostaining. **Results:** LTD-like reduction (DCS-LTD) of excitatory synaptic strength was reliably induced in superficial cortical layers by cathodal DCS, while an LTP-like effect (DCS-LTP) was observed in deep cortical layers below the stimulating site in mouse M1 slices. This heterogeneous pattern of altered synaptic strength was not found in pharmacologically induced LTD [by mGluR1/5 agonist R,S-dihydroxyphenylglycine (DHPG)] or LTP (by high Ca^{2+}). pS6 increased 1 hour after cathodal

tDCS in the cortical layer 2/3 and 5, but not in the deeper layers in mouse M1 slices. Consistent with the pS6 staining, we identified a selective inhibition of DCS-LTD by bath application of mGluR5 negative allosteric modulator, while DCS-LTP in the deeper layers was largely preserved. Cathodal DCS effects were non-uniform in either mouse or human neocortical slices, with patches of either unchanged or potentiated cortex mixed with DCS-LTD. However, cathodal DCS-LTD was uniform if DCS-LTP was blocked by NMDAR antagonist. **Conclusion:** DCS effects on cortical excitability are not uniform throughout the cortex, which may explain the weak cathodal tDCS effect in clinical trials. Human in vitro data indicate strong similarity between DCS effects in mouse and human neocortex. Since a uniform DCS-LTD effect across cortical layers was achieved by NMDAR block, we suggest a potential clinical use of NMDAR antagonism to enhance cathodal tDCS efficiency.

Disclosures: Y. Sun: None. **S.C. Dhamne:** None. **M.C. Goldenberg:** None. **J.R. Madsen:** None. **A. Rotenberg:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.08/F9

Topic: B.08. Synaptic Plasticity

Support: R01 ns073930

Title: Caspase-2 deficiency impairs pruning of dendritic spines and elevates anxiety

Authors: *Z. XU, J. TAN, H. XU, C. HILL, O. OSTROVSKAYA, K. MARTEMYANOV, B. XU
Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: Dendritic spines are the postsynaptic sites for the majority of excitatory synapses, and they are formed in excess during development. Pruning of excess spines is critical in the refinement of neuronal connections during establishment of an efficient and properly functional neural circuit; however, the molecular mechanism governing spine pruning remains largely unknown. Here we show that caspase-2, the most conserved but least known caspase, is essential for selective spine elimination in the hippocampus. We found that inhibition of caspase-2 activity with an inhibitor or knockdown of caspase-2 levels using an shRNA blocked spine pruning in cultured rat hippocampal neurons. In agreement with this in vitro observation, we found that spine density in hippocampal neurons was increased in caspase-2 knockout mice. We then examined the role of caspase-2 in hippocampal long-term depression (LTD), which is believed to be electrophysiological manifestation of spine pruning and involves internalization and degradation of synaptic AMPA receptor (AMPAR). We found that inhibiting caspase-2 blocked

AMPAR internalization during LTD induction and that caspase-2 knockout mice had elevated levels of hippocampal AMPAR and deficits in hippocampal LTD. Caspase-2 likely controls LTD by activating proteasomes that are essential for AMPAR internalization, because we found that basal proteasome activity in the hippocampus were decreased in caspase-2 knockout mice compared to WT littermates and caspase-2 could activate proteasomes in cultured neurons during LTD induction. The deficits in spine pruning and LTD is associated with abnormal behavior. A battery of behavioral tests found that caspase-2 knockout mice displayed higher levels of anxiety and enhanced contextual fear memory, compared with control mice. Therefore, our study reveals a signaling cascade from caspase-2 to proteasomes and its critical role in synaptic plasticity and animal behavior.

Disclosures: Z. Xu: None. **J. Tan:** None. **H. Xu:** None. **C. Hill:** None. **O. Ostrovskaya:** None. **K. Martemyanov:** None. **B. Xu:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.09/F10

Topic: B.08. Synaptic Plasticity

Title: Long-term depression of excitatory transmission in the lateral septum

Authors: *J. M. POWER, M. RADNAN, C. CHAICHIM
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Abstract: The dorsal lateral septum (dLS) is a hub in the regulation of mood and motivated behaviours. dLS neurons integrate excitatory synaptic inputs, primarily from hippocampus, and send inhibitory projections to brain regions involved in reward and the generation of motivated behaviour. Hippocampal-dLS synapses are plastic and high frequency stimulation has been shown to induce long-term potentiation of these synapses. Here we investigated long-term synaptic depression (LTD) in the dLS. Horizontal brain slices (400 µm) were prepared from c57bl/6 mice (5-7 wk) according to standard procedures approved by the UNSW Animal Care and Ethics Committee. Extracellular field excitatory synaptic potentials (fEPSP) were recorded using a wire electrode positioned in the caudal dLS and evoked via a bipolar stimulating electrode in the fimbria fibre bundle. Low frequency synaptic stimulation (LFS; 1 Hz 15 min) induced a long-lasting depression in slices prepared from female, but not male mice. 1 hour after LFS, the field potential amplitude was 92 ± 5% and 103 ± 5% of baseline in slices from female (n = 16) and male (n = 8) mice, respectively (female vs male p = 0.03). In females, LTD was not observed in the presence of the NMDA-receptor antagonist APV indicating a requirement for NMDA receptor activation. These results suggest that the cellular mechanisms underlying context-dependent behavioural selection may be sex specific.

Disclosures: **J.M. Power:** None. **M. Radnan:** None. **C. Chaichim:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.10/F11

Topic: B.08. Synaptic Plasticity

Support: The Competitive Allocation Fund and the Multidisciplinary Program for Elucidating the Brain Development from Molecules to Social behaviour (Fukui Brain Project) of University of Fukui

Takeda Foundation

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Novartis Foundation (For MS) and a Kakenhi

Title: Phosphoinositide-responsive Phldb2 regulates synaptic plasticity through glutamate receptors

Authors: ***M. XIE**[1,3,4,5], Y. ISHIKAWA[6], H. YAGI[7], H. MATSUZAKI[3,5], Y. FUKAZAWA[2,3], M. SATO[8,3,5]
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Abstract: Synaptic plasticity is fundamental for learning and memory. An early phase LTP, late phase LTP and LTD are synaptic events underlying the plasticity, whereas how they are regulated are not fully elucidated. Whereas the crucial involvement of various phosphoinositides for synaptic plasticity is demonstrated, missing downstream molecular entity prevents us from its clear understanding. Here we identified Phldb2, of which PH domain is one most sensitive to PIP_3, works as a phosphoinositide-sensitive mediator in the spine. Phldb2 bound to PSD95, CaMKII, GluA1 and GluA2. Our freeze-fractured replica immunolabeling study revealed that the deletion of Phldb2 impaired the postsynaptic expression of NMDA receptors and AMPA receptors. Since PI3K inhibition resulted in less-accumulated Phldb2 in the spine, it is likely that such synaptic components are recruited into the spine depending on PIP_3 via Phldb2. Moreover,

Phldb2 was essential for an interaction of NMDA receptor and CaMKII, which is important for the induction and maintenance of LTP. Phldb2 also bound to AP2, which is crucial for AMPA receptor endocytosis. In the Phldb2 KO mice, long term memory formation as well as LTP and LTD was impaired. Together, Phldb2 is versatile but a key mediator sensing phosphoinositides for various phases of synaptic plasticity.

Disclosures: M. Xie: None. **Y. Ishikawa:** None. **H. Yagi:** None. **H. Matsuzaki:** None. **Y. Fukazawa:** None. **M. Sato:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.11/F12

Topic: B.08. Synaptic Plasticity

Support: NIA grant SC1AG046907

Title: Examining input-specific changes in medial prefrontal cortex plasticity

Authors: B. M. OWEN, *M. BENVENISTE
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Abstract: Memory impairment is often associated with depression. Substantial evidence in the literature suggests that synaptic plasticity may be involved in memory formation and storage. The medial prefrontal cortex (mPFC) is a region associated with both working memory and depression, and thus could be a locus for memory impairment. The mPFC receives inputs from distal brain regions including the hippocampus and amygdala that are also known to contribute to memory acquisition. These inputs may exhibit synapse-specific plasticity to different degrees. We examine the role of specific glutamatergic inputs in mPFC synaptic plasticity using optogenetic tools and a protocol that can induce long-term depression (LTD). Virus containing a channelrhodopsin construct (AAV-CaMKII-ChR2-eYFP) was injected into either the hippocampus or amygdala of male C57/Bl6 mice (P35-40). Four to-eight weeks later, brain slices containing the prelimbic (PL) and infralimbic (IL) regions were prepared, and whole-cell current clamp recordings were made from layer V neurons. EPSPs were evoked by 470 nm optical stimulation. Preliminary data indicates PL neurons undergo LTD following 1 Hz optical stimulation for 15 minutes. This work lays down the foundation for understanding how distal inputs integrate in the mPFC and influence plasticity at the cellular level.

Disclosures: B.M. Owen: None. **M. Benveniste:** None.

Poster

041. Long-Term Depression

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant 5R21MH110223-02

Title: Arc regulation and association with endocytic proteins in long-term depression

Authors: *Y. YU[1], B. M. S. S. GOO[1], B. BARYLKO[2], B. J. SANSTRUM[1], J. P. ALBANESI[2], N. G. JAMES[1]
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Abstract: Activity-regulated cytoskeleton-associated protein (Arc/Arg3.1) is rapidly induced in response to neuronal activity and plays a role in long-term depression (LTD) by increasing the internalization of AMPA receptors. Though Arc is known to associate with endocytic proteins, endophilin and dynamin, the precise mechanism by which Arc decreases the surface expression of AMPA receptors is largely undefined. Here we present evidence that Arc can also bind directly to phospholipids *in vitro*, and that the Arc-membrane interaction may be enhanced through interaction with other endocytic proteins. We used fluorescence fluctuation spectroscopy (FFS) to characterize Arc regulation in the cytosol and at the plasma membrane using two-photon confocal microscopy and total internal reflection fluorescence (TIRF) microscopy. We utilized raster image correlation spectroscopy (RICS), photon counting histogram (PCH), and number and brightness (N&B) analysis to verify and characterize Arc-protein interactions to further explain the regulation of Arc in SH-SY5Y cells. These results show that recombinant fluorescently-tagged Arc forms dynamic puncta at the membrane which may serve as an endocytic hub. Furthermore, we found that the oligomerization state of Arc is positively associated with Arc concentration. Ultimately, this study further explains how Arc regulates endocytosis by providing evidence that local protein concentration and protein interaction increases Arc association with the plasma membrane.

Disclosures: Y. Yu: None. **B.M.S.S. Goo:** None. **B. Barylko:** None. **B.J. Sanstrum:** None. **J.P. Albanesi:** None. **N.G. James:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

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Topic: B.08. Synaptic Plasticity

Support: MT-F: FCT/PhD Fellow (IMM-LisbonBioMed-PhD program SFRH/BD/52228/2013);

LVL: iFCT; PTDC/BIM-MEC/4778/2014; .

TFO: DFG Center for Nanoscale Microscopy and Molecular Physiology of the Brain

Title: Properties of long-term depression upon aging

Authors: *L. V. LOPES[1], M. TEMIDO-FERREIRA[1], D. G. FERREIRA[1], J. E. COELHO[1], T. F. OUTEIRO[2]
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Abstract: Memory is a balance between strengthening and weakening of synapses reflected by cellular and molecular events that occur during long-term potentiation (LTP) and and long-term depression (LTD) (Xia and Storm, 2005, Nat Rev Neurosci). Both processes are involved in information storage and therefore in learning and memory. Aging is associated with a decline in cognitive function that can, in part, be explained by changes in neural plasticity or cellular alterations that directly affect mechanisms of plasticity (Burke and Collingdrige et al, 2010; Barnes, 2006, Nat Rev Neurosci). Although LTP deficits are widely described to be associated to memory impairment, much less is known about LTD. Aging and Alzheimer's disease (AD) are associated with hippocampal alterations and cognitive impairments and to a an upsurge in $A_{2A}R$. Epidemiological data showed that regular caffeine consumption, a non-selective $A_{2A}R$ antagonist, decreases the risk of developing memory impairments in aging and AD (van Boxtel *et al*, 2003, Pharmacol. Biochem. Behav.; Ritchie *et al*, 2007, Neurology). Blocking $A_{2A}R$ in aging and AD models prevents, hippocampus-related impairments, namely LTP (Batalha *et al*, 2013, Mol. Psychiatry; Laurent *et al*, 2015, Mol. Psychiatry; Vieira da Silva S, 2016, Nat Comm). Consequently, hippocampal $A_{2A}R$ function dysregulation is associated to some detrimental processes leading to aging and AD. Our aim was to evaluate LTD properties in an aging-like model with a neuronal-specific adenosine A_{2A} receptors ($A_{2A}R$) overexpression in forebrain [tg(CaMKII-h$A_{2A}R$)]. We performed field extracellular recordings in CA1 hippocampal neurons from tg(CaMKII-h$A_{2A}R$) *versus* wildtype animals. We then evaluated the consequences to synaptic plasticity in the Schaffer collaterals - CA1 synapse: a low frequency stimulation train not only failed to induce long-term depression (LTD) in tg(CAMKII-h$A_{2A}R$), as

compared to WT animals, but instead potentiated the CA3/CA1 synapse. This shift in LTD was rescued by $A_{2A}R$ blockade and was due to NMDA differential activation. We then probed this mechanism in aged (18 months-old) *versus* young (3-4 months old) rats. We found a similar shift in LTD in aged animals presenting cognitive and memory deficits that was rescued by blocking $A_{2A}R$ activation.Altogether, these data show that $A_{2A}R$ overexpression (characteristic of AD and aging human brain) causes NMDAR overactivation leading to LTD disruption, which may underlie age-associated memory deficits and be a key event leading to AD synaptic dysfunction.

Disclosures: L.V. Lopes: None. **M. Temido-Ferreira:** None. **D.G. Ferreira:** None. **J.E. Coelho:** None. **T.F. Outeiro:** None.

Poster

041. Long-Term Depression

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Program#/Poster#: 041.14/G3

Topic: B.08. Synaptic Plasticity

Support: KAKENHI17H03557

Title: Drebrin plays a role in mGluR-dependent LTD

Authors: *T. SHIRAO[1], K. HANAMURA[2], H. YASUDA[2], Y. SEKINO[3], N. KOJIMA[4]
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Abstract: Drebrin forms a stable structure with F-actin at postsynaptic sites od dendritic spines. We have shown that myosin-II mediated drebrin-actin exodus is an initial event in LTP formation (For a review see Shirao et al. J. Neurochem., 2017). The embryonic isoform, drebrin E, is expressed in the embryonic and early postnatal brain, and is replaced with the adult isoform, drebin A, during neuronal development although the functional difference between drebrin isoforms has not been well elucidated. In this study, we measured the dynamics of GFP-tagged drebrin E (GFP-DE) and drebrin A (GFP-DA) in cultured hippocampal neurons by fluorescence recovery after photobleaching analysis. We found that GFP-DA has a larger stable fraction than GFP-DE. The stable fraction was dependent on the drebrin A-specific sequence “Ins2”, located in the middle of the drebrin protein. In addition, F-actin depolymerization with latrunculin A significantly reduced the stable GFP-DA fraction. These findings indicate that the accumulation of stable F-actin in dendritic spines is mediated by a drebrin isoform conversion, which plays a pivotal role in synapse formation. To examine the difference in the physiological role between drebrin E and drebrin A, we analyzed drebrin A-specific knockout (DAKO) mice in which the isoform conversion of drebrin E to A was disrupted. We found that drebrin isoforms

differentially regulate the induction of long-term depression (LTD). While low-frequency stimulation (LFS) induced NMDA receptor (NMDAR)-dependent LTD in the developing hippocampus in wild-type mice, LFS induced robust metabotropic glutamate receptor 5 (mGluR5)-dependent LTD in both developing and adult brains of DAKO mice. Although agonist-induced mGluR-dependent LTD was normal in either wild-type or drebrin null knockout mice, it was enhanced in DAKO mice, suggesting that abnormally expressed drebrin E in adult brain lowers the threshold of mGluR5-dependent LTD. Thus, developmental conversion from drebrin E to drebrin A prevents robust mGluR5-dependent LTD in the adult brain.

Disclosures: **T. Shirao:** None. **K. Hanamura:** None. **H. Yasuda:** None. **Y. Sekino:** None. **N. Kojima:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.15/G4

Topic: B.08. Synaptic Plasticity

Support: the National Research foundation of Korea 2014051826

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Title: Identification of postsynaptic phosphatidylinositol-4,5-bisphosphate (PIP2) roles for synaptic plasticity using chemically induced dimerization

Authors: *M.-J. JEONG, H.-J. JO, S.-J. KIM, J. JUNG, J.-H. KIM
POSTECH, Nam-Gu, Pohang-Si, Gyeongbuk, Korea, Republic of

Abstract: Phosphatidylinositol-4,5-bisphosphate (PIP2), one of the key phospholipids, directly interacts with several membrane and cytosolic proteins at neuronal plasma membranes, leading to changes in neuronal properties including the feature and surface expression of ionotropic receptors. Although PIP2 is also concentrated at the dendritic spines, little is known about the direct physiological functions of PIP2 at postsynaptic as opposed to presynaptic sites. Most previous studies used genetic and pharmacological methods to modulate enzymes that alter PIP2 levels, making it difficult to delineate time- or region-specific roles of PIP2. We used chemically-induced dimerization to translocate inositol polyphosphate 5-phosphatase (Inp54p) to plasma membranes in the presence of rapamycin. Upon redistribution of of Inp54p, long-term depression (LTD) induced by low-frequency stimulation was blocked in the mouse hippocampal

CA3-CA1 pathway, but the catalytically-dead mutant did not affect LTD induction. Collectively, PIP2 is critically required for induction of LTD whereas translocation of Inp54p to plasma membranes has no effect on the intrinsic properties of the neurons, basal synaptic transmission, long-term potentiation or expression of LTD.

Disclosures: **M. Jeong:** None. **H. Jo:** None. **S. Kim:** None. **J. Jung:** None. **J. Kim:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.16/G5

Topic: B.08. Synaptic Plasticity

Support: NIH Grant NS088453

Title: The $GABA_B$ agonist baclofen persistently depresses inhibitory synapses in the rostral agranular insular cortex

Authors: *R. J. STEVENSON[1], J. A. KAUER[2]
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Abstract: The insular cortex is involved in interoception, including pain perception. Elevation of GABA levels in the rostral agranular insular cortex (RAIC) of mice produces analgesia, and subsequent microinjections of a $GABA_B$ receptor ($GABA_BR$) antagonist to the same site disinhibit a projection to the basolateral amygdala (BLA) and produce hyperalgesia (Jasmin et al 2003; Nature 424: 316). $GABA_BR$ activity in this area may therefore play an important role in limiting pain perception, possibly by decreasing cell excitability and/or altering synaptic input to RAIC pyramidal cells involved in pain pathways. We used patch-clamp recordings of layer 5 pyramidal cells, which include a large population of BLA-projecting cells, in acute slices of mouse RAIC to test the role of $GABA_BR$ on inhibitory inputs to these neurons. 5 uM baclofen decreased the amplitude of inhibitory post-synaptic currents (IPSCs) by 64% +/- 5.6 at ten minutes (n=8). This effect is reliably observed with IPSCs evoked by local electrical stimulation, and can also be seen with IPSCs evoked by local optogenetic stimulation of parvalbumin-expressing interneurons (n=1 of 2). Baclofen exposure increases the paired pulse ratio of IPSCs, suggesting that a decrease in presynaptic release mediates the depression, likely through $GABA_BR$ on presynaptic terminals. The baclofen-induced depression persists, with IPSC amplitudes remaining at 53.3% +/- 25.1 of baseline values during minutes 17-19 of washout. Although $GABA_BR$ labeling was reported in less than 40% of cells in each layer 5 pyramidal population (Ohara et al 2003; J Neurocytol 32:131), we have observed baclofen-induced outward currents in every layer 5 pyramidal cell recorded (n=27). Next, we will determine whether

baclofen-induced synaptic depression persists after antagonism of $GABA_BR$ activity, whether baclofen alters excitatory inputs to these neurons, whether baclofen effects are expressed differently among inhibitory neuron populations, and the mechanism behind these effects. As the balance of excitation and inhibition has a demonstrated impact on insular cortex functions, exploring the ways $GABA_BR$ activity shapes synaptic transmission will be important to understanding this under-investigated region.
Supported by NS088453 (JAK) and Diversity Supplement NS088453 (RJS).

Disclosures: R.J. Stevenson: None. **J.A. Kauer:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.17/G6

Topic: B.08. Synaptic Plasticity

Support: NARSAD 2014 Young Investigator Grant

Title: Neuregulin 1/ErbB signalling controls hippocampal mGluRI-dependent synaptic plasticity and related cognitive functions

Authors: *A. LEDONNE[1], D. MANGO[2], E. C. LATAGLIATA[1], G. CHIACCHIERINI[3], A. NOBILI[1,4], R. NISTICÒ[2,5], M. D'AMELIO[1,4], S. PUGLISI-ALLEGRA[1,3], N. B. MERCURI[1,5]
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Abstract: The neurotrophic factor Neuregulin 1 (NRG1) and its receptors, ErbB tyrosine kinases, regulate neurotransmission, synaptic plasticity and cognitive functions and their alterations have been associated to different neuropsychiatric disorders. Indeed, NRG1 and ErbB receptors represent candidate susceptibility genes for schizophrenia, and their dysfunction has been also reported in bipolar disorder, autism-spectrum disorders, ADHD and Alzheimer's disease. It is well established that Group 1 metabotropic glutamate receptors (mGluRI) control neuronal activity and synaptic transmission, thus affecting learning and memory, as well as complex behaviors. Emerging evidence suggest a key role for mGluRI in neuropsychiatric disorders, since their dysfunction is supposed to cause synaptic, behavioral and cognitive deficits linked to various diseases, like autism-spectrum disorders, intellectual disabilities and schizophrenia. Recently we have demonstrated a functional interaction between NRG1/ErbB signalling and mGluRI in mesencephalic DAergic neurons, that controls DAergic transmission *in vivo* (Ledonne et al., 2015, Mol Psychiatry 20:959-973). Besides this evidence, the relationship between NRG1/ErbB signalling and mGluRI-dependent mechanisms is still uncharacterized. Here, we investigated the role of NRG1/ErbB signalling on the modulation of mGluRI functions

in hippocampal CA1 pyramidal neurons, by means of electrophysiological recordings in hippocampal rodent slices. In particular, we analysed the involvement of NRG1/ErbB receptors on mGluRI-dependent regulation of pyramidal neurons activity and glutamatergic synaptic plasticity at CA3-CA1 synapses. Moreover, we evaluated the role of hippocampal NRG1/ErbB signalling on object recognition memory, a behavioral learning task strictly dependent on hippocampal mGluRI. Our results reveal that NRG1/ErbB signalling is a critical modulator of mGluRI function in hippocampal CA1 pyramidal neurons, thus affecting neuronal excitability and glutamatergic synaptic plasticity at CA3-CA1 synapses as well as hippocampal mGluRI-dependent aspects of learning and memory. Since a dysfunction in NRG1/ErbB signalling represents a shared event of several neuropsychiatric disorders also characterized by hippocampal mGluRI-dependent synaptic and cognitive deficits, the functional interaction between hippocampal NRG1/ErbB receptors and mGluRI, here reported, might have important implications in different brain diseases.

Disclosures: **A. Ledonne:** None. **D. Mango:** None. **E.C. Latagliata:** None. **G. Chiacchierini:** None. **A. Nobili:** None. **R. Nisticò:** None. **M. D'Amelio:** None. **S. Puglisi-Allegra:** None. **N.B. Mercuri:** None.

Poster

041. Long-Term Depression

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 041.18/G7

Topic: B.08. Synaptic Plasticity

Support: NS070301

DA035430

NS090903

Title: Pin1 regulates PSD-95 ubiquitination and its stability at excitatory synapses

Authors: ***J. Y. DELGADO**[1], A. MCLEOND[2], D. L. NALL[3], P. R. SELVIN[3], P. F. WORLEY[4], W. N. GREEN[5]
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Abstract: Proline-directed protein phosphorylation is an essential step for the induction of NMDA-dependent long-term synaptic depression (LTD). Central to the induction of LTD is the phosphorylation of Postsynaptic Density Protein 95 (PSD-95) by the Glycogen Synthase 3 β of

Threonine 19 and subsequent down regulation at the synapse. However, the mechanism linking proline-directed phosphorylation to the stability of PSD-95 at synapses is not understood. Here, we present data suggesting that PSD-95 proline-directed phosphorylation sites, threonine 19 and serine 25, recruit binding of phosphorylation-dependent peptidyl-propyl cis/trans isomerize 1 (Pin1). Pin1 has been shown to interact with S287, T290 and T295 within the hinge domain of PSD-95 and positively regulate N-Methyl-D-Aspartate receptors (NMDARs) content at synapses1. At the molecular level, Pin1 binding is thought to trigger a conformational change in PSD-95 that regulates downstream posttranslational modifications. In this presentation, we will present data showing that Pin1 facilitates PSD-95 ubiquitination. In addition, we examine the effect of Pin1 on synapse number, and PSD-95 localization via confocal microscopy and superresolution microscopy, AMPAR receptor mobility by single particle tracking experiments and excitatory synaptic transmission. We present evidence supporting the importance of Pin1 in control of PSD-95 and maintenance of stable synapses.
1.Antonelli, R. et al. Pin1 Modulates the Synaptic Content of NMDA Receptors via Prolyl-Isomerization of PSD-95. J. Neurosci. 36, 5437-5447 (2016).

Disclosures: **J.Y. Delgado:** None. **A. McLeond:** None. **D.L. Nall:** None. **P.R. Selvin:** None. **P.F. Worley:** None. **W.N. Green:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.01/G8

Topic: B.12. Glial Mechanisms

Support: KAKENHI 26117520, 16H01888 (HH)

KAKENHI 25221002 (KM)

KAKENHI 26282222, 17H02221 (YS)

HFSP (RGP0036/2014)

Title: Rearing-environment-dependent hippocampal LFP differences in wildtype and IP_3R2-KO mice

Authors: *X. WANG[1], M. TANAKA[1], K. MIKOSHIBA[1], H. HIRASE[1,2], Y. SHINOHARA[1]
[1]RIKEN Brain Sci. Inst., Wako, Japan; [2]Brain and Body Syst. Sci. Inst., Saitama Univ., Saitama, Japan

Abstract: Rearing in an enriched environment (ENR) is known to enhance cognitive and memory abilities in rodents, whereas social isolation (ISO) induces depression-like behavior.

The hippocampus has been documented to undergo morphological and functional changes depending on these rearing environments. For instance, rearing condition during juvenility alters CA1 *stratum radiatum* gamma oscillation power in rats. In this study, hippocampal CA1 local field potentials (LFP) were recorded from bilateral CA1 in urethane-anesthetized mice that were reared in either ENR or ISO condition. Similar to previous findings in rats, gamma oscillation power during theta states was higher in ENR group. Ripple events that occur during non-theta periods in the CA1 *stratum pyramidale* also had longer intervals in ISO mice. Since astrocytic Ca^{2+} elevations play a key role in synaptic plasticity, we next tested if these changes in LFP are also expressed in IP_3R2-knockout (KO) mice, in which astrocytic Ca^{2+} elevations are largely diminished. We found that the gamma power was also higher in IP_3R2-KO-ENR mice compared to IP_3R2-KO-ISO mice, suggesting that the rearing-environment-dependent gamma power alternation does not necessarily require the astrocytic IP_3/Ca^{2+} pathway. By contrast, ripple events showed genotype-dependent changes as well as rearing condition-dependent changes: ISO housing and IP_3R2 deficiency both lead to longer inter-ripple intervals. Moreover, we found that ripple magnitude in the right CA1 tended to be smaller in IP_3R2-KO. Since IP_3R2-KO mice have been reported to have depression phenotypes, our results suggest that ripple events and animals' mood may be broadly correlated.

Disclosures: X. Wang: None. **M. Tanaka:** None. **K. Mikoshiba:** None. **H. Hirase:** None. **Y. Shinohara:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

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Topic: B.12. Glial Mechanisms

Support: KAKENHI 23650171, 25640017, 26117520, 16H01888, 16K13116,

HFSP RGP0036/2014

RIKEN Brain Science Institute

Title: Astrocytic control of neural activity and behavior by optogenetic Gq-coupled receptor activation

Authors: *Y. IWAI, K. OZAWA, K. YAHAGI, S. SATO, H. HIRASE
RIKEN Brain Sci. Inst., Wako-Shi, Japan

Abstract: Astrocytes express a wide variety of Gq-type G protein-coupled receptors (GPCRs) and respond to their agonists with intracellular Ca^{2+} elevations. Recent studies show that Gq-GPCR activation by neuromodulators strongly increases astrocytic Ca^{2+} and represents a major

mechanism for astrocytic Ca^{2+} dynamics *in vivo* (Bekar et al., 2008; Takata et al., 2011; Ding et al, 2013; Paukert et al, 2014). However, the functional significance of astrocytic Gq-GPCR signaling in neural activity and behavior modulation remains controversial (Agulhon et al, 2010), because studies by astrocyte-selective Gq-GPCR manipulation are limited. In order to specifically and dynamically activate astrocytic Gq-GPCR signaling *in vivo*, we have generated transgenic mice in which OptoA1AR-EYFP, an optically activatable Gq-GPCR (Airan et al., 2009), is expressed under the control of a BAC-GLT1 promoter. Among the transgenic lines established, several lines showed selective astrocytic expression, with differences observed in their expression strength and positive astrocytic proportion. Cortical GFAP expression appeared generally low, suggesting that the expression of OptoA1AR does not cause glial inflammation. We confirmed that astrocytic Ca^{2+} elevation was triggered by brief illumination of blue light (~1 s) in anesthetized conditions. The magnitude of optically-evoked Ca^{2+} surges was comparable to that of spontaneous Ca^{2+} activities. This optical activation was repeatable, as a non-stimulus period of ~3 min restored the original response magnitude. Remarkably, stronger optical stimulation could induce astrocytic Ca^{2+} wave propagation, in which Ca^{2+} elevations were observed in OptoA1AR-negative astrocytes with a delay of several seconds after the activation of the neighboring OptoA1AR-positive astrocytes. Furthermore, the surrounding neurons were also found to be rapidly activated following the astrocytic optical stimulation. Preliminary results suggest that optogenetic activation in the prefrontal cortical area enhances long-term memory evaluated by object recognition test, whereas short-term memory evaluated by Y-maze test is not changed. During object familiarization period, transgenic and wild-type mice spent similar amounts of time in contacting two novel objects upon brief blue-light illuminations. When one of the pre-exposed objects was replaced with a different object 3-days or 14-days later, transgenic mice tended to spend a longer time in contacting the replaced object. We are currently exploring molecular mechanisms underlying this behavioral change.

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Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.03/G10

Topic: B.12. Glial Mechanisms

Support: VR

Title: Hippocampal metabolic and synaptic neuro-glial dysfunction after peripheral trauma

Authors: ***M. GOMEZ-GALAN**[1], T. FEMENÍA[1], A. GIMENEZ-CASSINA[2], S. CODELUPPI[2], L. ERIKSSON[1]

[1]Physiol. and Pharmacol., Karoliska Inst., Stockholm, Sweden; [2]Karolinska Institutet, Stockholm, Sweden

Abstract: Long-term cognitive impairment after peripheral surgery is a common and serious complication particularly in the elderly population. While there are growing body of evidence suggesting that surgery-induced inflammation play a key role behind this surgical phenotype, the pathogenesis within the central nervous system is not fully understood.
In surgical animal models, surgery is associated with a transient disruption of the blood-brain-barrier that facilitates peripheral macrophages to migrate into the hippocampus, subsequently promoting brain immune activation with later cognitive impairment at 72h (Terrando et al., 2011). In humans, similar dynamic changes in brain immune system have recently been confirmed (Forsberg et al, Annals Neurol 2017). To further understand the temporal pattern of immune activation and simultaneous changes in synaptic transmission within hippocampal neuronal circuits of relevance for cognitive processing, we investigated the effect of rodent surgery on neuronal-glial function combining calcium imaging in astrocytes and whole-cell patch clamp in CA1 pyramidal cells with molecular tools.
Accordingly with the notion of a peripheral-brain communication after systemic trauma, we detected an increased in the proinflammatory cytokine IL-6 at 6h after tibia fracture, returning to normal by 72h. We also found dynamic changes in the microglia markers, IBA1 and CX3CR1, and a profound decrease in the astrocytic markers, GFAP and AQP-4, at 24h and 72h post-trauma. Notably, these astrocytic alterations were accompanied with loss of Ca^{2+} signaling at 24h, with any impact on neuronal function.
Conversely/ However, at 72h post-trauma, when the cognitive decline occurs, the frequency and amplitude of the excitatory post-synaptic currents from CA1-pyramidal cells were increased vs. naïve-mice. Likewise, synaptic protein levels and astrocyte glutamate transporters were also affected at 72h. Finally, lactate, an essential energy substrate that is produced by the astrocytes and critical for memory formation, showed temporal fluctuations during the 72h period after surgery. Lactate fluxes were accompanied with changes in the main astrocyte and neuronal lactate and glucose transporters thereby highlighting an aberrant astrocyte/neuronal metabolic coupling that potentially may underlie cognitive dysfunction in this model.
All together, our findings confirm an interaction between the peripheral and central immune system and uncover a role for the astrocyte as a mediator between systemic immune and inflammatory events and synaptic neuronal functions and processing, such as cognition.

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Poster

042. Effects of Neuron and Glia Interaction

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Topic: B.12. Glial Mechanisms

Support: NIH Grant MH097957-02

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CURE PA Dept of Health

NIH Grant MH110724-01

Title: Sonic hedgehog signaling in astrocytes is required for organizing cortical microcircuitry

Authors: *A. S. BLAESER[1], S. A. HILL[1], A. COLEY[2], W. .-J. GAO[2], A. D. R. GARCIA[1]
[1]Biol. Dept, Drexel Univ., Philadelphia, PA; [2]Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Astrocytes play a critical role in synaptogenesis, as well as synaptic function and plasticity throughout life. We previously identified a subpopulation of neocortical astrocytes expressing the Sonic hedgehog (Shh) target gene Gli1 in the adult brain. A subpopulation of neurons in layer V express Shh, suggesting a novel form of neuron-astrocyte communication in the mature cortex. While the precise role of Shh signaling between neurons and astrocytes remains to be determined, non-canonical Shh signaling between neurons in the early postnatal cortex is required for establishing local microcircuitry. Whether neuron-astrocyte Shh signaling also plays a role in the development or maintenance of cortical synapses is unknown. In this study, we examined the role of canonical Shh signaling in astrocytes on synaptic architecture, plasticity and function of layer V pyramidal neurons in primary somatosensory cortex. We selectively disrupted Shh activity in astrocytes by conditional knock out (CKO) of the obligatory Shh coreceptor Smoothened (Smo) in GFAP-Cre Smo floxed mice (SmoCKO). Our results show that these mice exhibit an increase in spine density on apical tuft dendrites in neocortex but not hippocampus, where Gli1-expressing astrocytes are rare. This density phenotype emerges during postnatal development and is maintained into adulthood. *In vivo* chronic imaging of these dendrites suggests that this phenotype results from increased synaptic stability in SmoCKO mice relative to controls. Furthermore, the increase in spine density is also accompanied by an increase in the frequency of excitatory postsynaptic currents, as measured by whole-cell electrophysiology in acute slices. Together, these results identify a novel, Shh-dependent neuron-astrocyte-neuron interaction that regulates cortical microcircuitry during development and throughout adulthood.

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Poster

042. Effects of Neuron and Glia Interaction

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Topic: B.12. Glial Mechanisms

Support: NIH Grant R21NS087391

NIH Grant R21DA042342

Title: *In vivo* exosome-mediated neuron to glial signaling in the CNS

Authors: *R. JARVIS, E. BROWN, S. JIN, M. CHIANG, Y. YANG
Neurosci., Tufts Univ., Boston, MA

Abstract: Exosomes are small (40-100 nm) membrane-bound vesicles which are secreted by most cell types, including CNS cells. Exosomes can contain a variety of molecules, including mRNAs, proteins, and miRNAs, and can fuse with neighboring cells to release their contents, serving as a mode of intercellular signaling. It is becoming evident that exosomes may play an important role in facilitating disease pathology. However, most studies of exosomes have been done using *in vitro* cell culture, which is disconnected from *in vivo* physiology and pathology. Therefore, it is crucial to understand the *in vivo* characteristics, distribution, and behavior of exosomes within the CNS. We have generated a novel Cre-inducible CD63 exosome reporter mouse, which allows GFP labeling of endogenous exosomes *in vivo*. Our model is based on the Cre-LoxP recombination system, with a floxed stop codon upstream of GFP-tagged CD63. When induced with a specific promoter-driven Cre recombinase, GFP-CD63-expressing exosomes are labeled in a cell type specific manner. To validate the system, we stereotaxically injected the cortex of GFP-CD63/Ai14 mice with either AAV8-CAMKII-Cre virus (neuronal promoter) or AAV5-GFAP-Cre virus (astrocyte promoter), and observed GFP-expressing puncta in cell types specific to the promoter used. These puncta were detected both intracellularly and extracellularly of the parent cells (as visualized by Cre-activated tdTomato expression from Ai14 mice). The GFP-CD63 puncta were confirmed to be exosomes by immunohistochemistry staining against common exosome markers. We also observed that, following a focal Cre virus injection, GFP-labeled exosomes migrated considerable distances - up to several µm, and even to the cervical spinal cord - from the tdTomato expressing cells of origin. This result highlights the potential for exosomes to propagate across large areas of the CNS. In summary, we have developed and validated a novel knock-in mouse model that enables the cell type-specific labeling of endogenous exosomes with GFP-CD63. This system offers a new and invaluable tool in deciphering the function of exosomes in the CNS physiology, as well as elucidating the role of exosomes in neurodegenerative diseases.

Disclosures: **R. Jarvis:** None. **E. Brown:** None. **S. Jin:** None. **M. Chiang:** None. **Y. Yang:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

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Program#/Poster#: 042.06/H3

Topic: B.12. Glial Mechanisms

Title: Notch-independent Delta signaling in glia regulates synaptic function at the *Drosophila* neuromuscular junction

Authors: *M. R. CALDERON[1], G. KAUWE[2], P. HAGHIGHI[3]
[1]The Buck Inst. For Res. On Aging, Novato, CA; [2]Buck Inst. Res. On Aging, Novato, CA; [3]Buck Inst. for Res. on Aging, Novato, CA

Abstract: A growing body of evidence indicates that glia play critical roles in nervous system function from proper development and wiring of the brain to establishment of memory and higher brain functions; nevertheless, our understanding of the molecular details of interactions between glia and neurons remains limited. To address this unmet need, we took advantage of the powerful genetic tools available in Drosophila melanogaster to conduct an RNAi screen in third instar larvae for glial ligands that may affect synaptic structure or function at the neuromuscular junction (NMJ). Our results show that transgenic glial knockdown of the ligand Delta, while having no effect on NMJ synaptic structure, caused a strong reduction in synaptic function. Surprisingly, our genetic experiments did not support a role for Notch in mediating the effect of Delta, suggesting that Delta likely acts through a cell autonomous and non-canonical mechanism in glia. As delta has an important role in early embryonic developmental processes, we performed additional experiments by knocking down Delta only during larval stages. Transgenic knockdown of Delta only during larval stages resulted in a similar reduction in neurotransmitter release, further supporting that transsynaptic regulation by glia is critical to establish the normal set point for neurotransmitter release. We will present our ongoing experiments aimed at identifying additional molecular players in establishing this critical link between glia and motoneuron function. Our discovery has revealed a novel role for non-canonical Delta signaling that allows trans regulation of neuronal function via glia at the NMJ synapse.

Disclosures: **M.R. Calderon:** None. **G. Kauwe:** None. **P. Haghighi:** None.

Poster

042. Effects of Neuron and Glia Interaction

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Topic: B.12. Glial Mechanisms

Support: Research Council of Norway

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Title: Calcium signals in astrocytes during sleep

Authors: *L. BOJARSKAITE, D. M. BJØRNSTAD, R. ENGER, W. TANG, G. MORENO, R. LANTON, K. G. A. VERVAEKE, E. A. NAGELHUS
Univ. of Oslo, Inst. of Basic Med. Sci., Oslo, Norway

Abstract: The brain lacks lymphatic vessels and waste products are proposed to be cleared along paravascular “glymphatic” pathways (Iliff J.J. et al., Science Translational Medicine, 2012, 4(147), 147ra11). Glymphatic waste clearance is dependent on glial water channels and is twice as efficient during sleep than in the awake state (Xie L. et al., Science, 2013, 342(6156), 373-377). However, the precise mechanisms that orchestrate brain waste clearance are still not known. We hypothesized that astrocytic calcium signaling differs during wakefulness and sleep and potentially regulates glymphatic fluid flow. We used two-photon microscopy combined with chronic cranial windows and virally delivered genetically encoded calcium sensors to characterize astrocytic calcium signals in the cortex of sleeping or awake mice. Preliminary data indicate that astrocytic calcium signaling is suppressed during sleep. Resolving the mechanisms involved in brain waste removal is important for our understanding of a number of neurodegenerative disorders, including dementia and Alzheimer's, and may pave the way for new treatment strategies.

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Poster

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Title: Specific GABAergic interneurons evoke unique responses in cortical astrocytes

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Abstract: The signaling specificity to postsynaptic neurons of the different GABAergic interneuron subtypes is crucial to the generation of the functional heterogeneity that characterizes brain circuits. Whether the specificity of interneuron signaling applies also to other brain cells, such as the glial cell astrocytes, remains, however, poorly explored. To address this issue, we applied an adeno-associated virus-based strategy that induced in Parvalbumin- and Somatostatin-expressing interneurons, i.e., two key interneurons in the neocortex, a selective expression of the light-gated cation channel channelrhodopsin-2 and in astrocytes a sparse expression of the genetically encoded calcium indicator GCaMP6f. Using optogenetics and two-photon imaging in the mouse somatosensory cortex, both in *in vivo* and bran slice preparations, we reveal that the synaptic release of GABA upon the optogenetic activation of Parvalbumin or Somatostatin interneurons induces different astrocytic responses, expecially at the level of the fine processes. Interestingly, Parvalbumin interneuron signaling evokes a weak and depressing calcium response

while somatostatin interneuron signaling elicits a robust response that potentiates upon successive stimulations. Our study reveals a previously unidentified signalling specificity between interneuron subtypes and astrocytes which opens a new perspective into the role of astrocytes as distinct functional components of neocortical inhibitory circuits.

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Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.09/H6

Topic: B.12. Glial Mechanisms

Support: CIHR Grant 14392

Title: The astrocytic protein S100ß modulates Nav 1.6-dependent firing in layer 5 pyramidal neurons of the mouse visual cortex

Authors: ***D. RYCZKO**[1,2], B. J.-B. BRÉANT[3], M. HANINI-DAOUD[2], A. KOLTA[4]
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Abstract: Growing evidence indicate that astrocytes influence neural activity through release of different molecules in the extracellular space. Our recent work showed that astrocytes and their protein S100ß are responsible for rhythmogenesis in neurons of the chewing Central Pattern Generator (CPG) in the brainstem of rats (Morquette et al. Nat Neurosci 18:844-54). S100ß, a Ca^{2+}-binding protein, decreases the extracellular concentration of Ca^{2+}($[Ca^{2+}]_e$) and by doing so, activates a persistent sodium current in the CPG neurons, causing a switch in their firing pattern from a tonic to a rhythmic mode. It is unclear whether this mechanism is unique to CPG neurons or could also be present elsewhere in the brain. To address this issue we examined the effect of S100ß (129 µM) on layer 5 pyramidal neurons of the mouse visual cortex using whole cell recordings. Near resting membrane potentials (RMP; -50 to -65 mV), local applications of S100ß onto the recorded cell evoked a spiking activity (n = 7) with longer applications leading to higher firing frequencies (n = 3). At more hyperpolarized potentials (-65 to -80 mV), S100ß elicited rhythmical bursting (n = 3) indicating that decreases of $[Ca^{2+}]_e$ changes the neuron firing pattern as a function of its membrane potential. These effects of S100ß were reproduced with local applications of BAPTA (5 or 10 mM) a Ca^{2+}-chelator. As was the case with CPG neurons, these

effects of BAPTA and S100ß involved a persistent sodium current since bath applications of the Nav 1.6 channel blocker 4,9-anhydrotetrodotoxin reduced the spiking activity evoked by S100ß (n = 5) or BAPTA (n = 3). To examine how S100ß modified the transfer function of cortical neurons, trains of stimulation were applied in layer 1 at different frequencies (1-50 Hz). Pyramidal neurons rapidly adapted their firing pattern to increasing stimulation frequencies. Local applications of S100ß overrode this adaptation and increased spiking (n = 3). Using immunofluorescence experiments, we found that Nav 1.6 channels were distributed within the cell body and along the apical dendrite of layer 5 pyramidal neurons (n = 4). Cells immuno-positive for S100ß were found around neuronal cell bodies. Because many of these S100ß-positive cells were positive for glial fibrillary acidic protein (n = 2), these are likely astrocytes. Our results show that the astrocytic Ca^{2+} binding protein S100ß controls neural firing through activation of Nav 1.6 channels in the cortex. Our next goal is to identify the conditions that could induce release of S100ß from astrocytes in this region.

Disclosures: D. Ryczko: None. **B.J. Bréant:** None. **M. Hanini-Daoud:** None. **A. Kolta:** None.

Poster

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Topic: B.12. Glial Mechanisms

Support: 1F31NS093751-01

Title: $G_{i/o}$ protein-coupled receptors inhibit neurons but activate astrocytes and stimulate gliotransmission

Authors: *C. DURKEE, A. COVELO, S. JAMISON, A. ARAQUE
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Abstract: Astrocytes express neurotransmitter receptors that detect synaptically-released neurotransmitters, resulting in a calcium increase and a downstream release of gliotransmitters. Astrocytes express both G_q and $G_{i/o}$ G protein-coupled receptors (GPCRs). In neurons, G_q activation results in phospholipase C (PLC)-mediated excitation in form of depolarization and intracellular calcium elevations, whereas $G_{i/o}$ activation inhibits adenylyl cyclase and reduces cAMP, which results in cellular inhibition. While G_q-PLC activation is well known to activate astrocytes through calcium elevations, the effects of $G_{i/o}$ signaling is yet largely undetermined. To better characterize the effects of activating G_q- and $G_{i/o}$-linked intracellular cascades in neurons and astrocytes, we used a chemogenic approach using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). DREADDs adeno-associated viruses were targeted to neurons or astrocytes (using CaMKIIα or GFAP promoters, respectively) and carried either

G_q- or $G_{i/o}$-linked GPCRs (hM3D or hM4D, respectively). We measured changes in hippocampal neuronal excitability and astrocytic calcium via activation of either G_q or $G_{i/o}$ GPCRs using ACh and GABA, respectively. We found that G_q activation in both neurons and astrocytes led to cellular activation. In neurons, G_q activation induced inward currents, membrane depolarization, and action potential firing facilitation. In astrocytes, G_q activation induced calcium increases in both soma and processes. However, we found that in contrast to cellular inhibition in neurons after $G_{i/o}$ activation, $G_{i/o}$ activation in astrocytes also led to calcium increases. Additionally, astrocytic activation by either G_q or $G_{i/o}$ GPCRs in turn increased excitability in nearby neurons in the form of NMDAR-mediated slow inward currents and firing facilitation, suggesting the release of gliotransmitters downstream of calcium elevations. These results indicate that while activation of the different GPCR pathways in neurons led to either excitation or inhibition, astrocyte activation by both G_q and $G_{i/o}$ GPCR pathways led to excitation.

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Poster

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Topic: F.05. Neuroimmunology

Support: NIH RO1 MH096484-04

Title: Microglial clearance of neuronal debris following CNS injury is mediated by complement in an activity-independent manner

Authors: *G. NORRIS[1], A. J. FILIANO[2], J. KIPNIS[2]
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Abstract: Recent research has demonstrated a role for glial cells in the process of synaptic pruning and brain development of the lateral geniculate nucleus (LGN). This process was shown to occur during a distinct developmental window, with both microglia and astrocytes seen engulfing presynaptic material. Importantly, these works showed a critical need for both the complement system and neuronal activity for optimal synaptic pruning. Here we report that following optic nerve crush injury in adult mice there is significant neuronal degeneration in the LGN accompanied by activation of microglia and engulfment of presynaptic debris. Similar to development, we observe that the complement system is also employed in response to injury, with microglia playing a key role in C1q deposition. Additionally, we have observed by RNA sequencing that LGN microglia display a dynamic transcriptional profile in response to optic nerve crush. Further, microglial clearance of neuronal debris following CNS injury also functions independently of neuronal activity, distinguishing engulfment of injured neuronal

debris from developmental pruning. Together, these findings suggest mechanisms for both the activation and proliferation of microglia by damaged neuronal material as well as providing a mechanism for clearance of neuronal debris by microglia following CNS injury.

Disclosures: G. Norris: None. **A.J. Filiano:** None. **J. Kipnis:** None.

Poster

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Topic: B.12. Glial Mechanisms

Support: NINDS 1R21NS087391

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Title: Neuronal exosomal miR-124 as a master regulator of astrocytic GLT1 expression

Authors: *J. M. YELICK
Tufts Univ., Boston, MA

Abstract: Neuron to astrocyte signaling is essential for functional tripartite synapses in the mammalian central nervous system. Previous studies in our lab have shown that neuronal cultures secrete exosomes containing miR-124, which is capable of increasing GLT1 protein expression. To determine the function by which miR-124 increases GLT1, we transfected miR-124 into primary cultured astrocytes. qRT-PCR comparison of glt1a, glt1b, and glt1c expression levels showed that miR-124 increased all three isoforms, particularly glt1a. In addition to increased transcription of glt1, we found that miR-124 also decreased expression levels of several miRs of which were predicted to bind to the glt1 3' untranslated region (UTR). We screened these candidates by transfecting primary cultured astrocytes with miR mimics, resulting in three candidates that reproducibly decreased GLT1 protein expression; miRs-132, 218, and 128. miR-132 transfection had no effect upon glt1 mRNA expression via qRT-PCR, and cloning of its seed region of the glt1 3' UTR into a luciferase construct showed that miR-132 was capable of binding and inhibiting translation, defining miR-132 as a post-transcriptional inhibitor of glt1. miR-128 treated cells showed decreased expression of glt1 mRNA, while luciferase assays showed effective binding of miR-128 to glt1, suggesting that miR-128 binds and promotes glt1 transcript degradation. miR-128 transfection also decreased expression of glt1 mRNA, however luciferase assays showed no effect upon miR-128 addition. This shows that miR-128 indirectly diminishes GLT1 protein and transcript. To investigate if there is altered miR secretion in disease, we injected fluorescent miR-124 into mid-stage SOD1 G93A mice, a common model for Amyotrophic Lateral Sclerosis (ALS). We found increased secretion of miR-

124 from motor neurons and internalization into ALDH1-eGFP astrocytes, suggesting that miR-124 is a means by which neurons attempt to upregulate GLT1 in a GLT1-deficient state. In addition, fluorescent *in situ* hybridization of miR-124 in mid-stage SOD1 mice shows that endogenous miR-124 is decreased in spinal motor neurons. qRT-PCR of mid-stage SOD1 spinal cords showed reduced miR-124, further suggesting that miR-124 is released into the extracellular space in ALS. Our results identify that miR-124 has multiple functions to increase GLT1 expression, by increasing glt1 transcription as well as silencing GLT1-inhibiting miRs. In combination with our *in vivo* data showing increased secretion and loss of miR-124 from motor neurons, this suggests that neuronal miR-124 transfer to astrocytes is an important mechanism to restore GLT1 expression in ALS.

Disclosures: J.M. Yelick: None.

Poster

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Support: KAKENHI Grant JP26-1626

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Title: Estimation of effects after two-photon laser ablation on surrounding astrocytes by *In vivo* astrocytic Ca^{2+} imaging

Authors: *K. YAMAGUCHI, R. KAWAKAMI, T. NEMOTO
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Abstract: The brain is processing information by forming complicated neural networks. Although we know this fact, the information flows in the neural networks remain unclear. Recently, we have reported use of an advanced two-photon laser ablation to break down single neural processes within cortical layer V in living mouse brains (732.03, Neuroscience 2015). We have confirmed the increase of intracellular Ca^{2+} concentration in brain through by *in vivo* astrocytic Ca^{2+} imaging. However, the effects of the laser ablation on astrocytes surrounding the target processes are not yet clear. In order to observe neural processes and astrocytic $[Ca^{2+}]_i$ at the same time using fluorescence microscopy, we mated Thy1-eYFP-H and GLT1-GCaMP7-G7NG817 in a mouse strain. The new strain expresses a fluorescent protein eYFP in a part of

neurons and a Ca^{2+} indicator GCaMP7 mainly in astrocytes. After severing neural processes inside the brain of the mouse using two-photon laser ablation, increase of the astrocytic $[Ca^{2+}]_i$ around the target regions was observed even when the damaged area was restricted to very small. In contrast, no $[Ca^{2+}]_i$ increase was observed in the case of less cycles of laser irradiation number, which is not sufficient to induce severance. Evaluated the area of $[Ca^{2+}]_i$ increases quantitatively, we found that the area correlated with the cycles of laser irradiation number. This indicates that the cycles of laser irradiation number represent as applied energy to the target region, and serious effects on the surrounding astrocytes express as spreading area of $[Ca^{2+}]_i$ change after the laser ablation. On one hand, the surrounding astrocytic $[Ca^{2+}]_i$ change did not persist for 10 minutes after the laser ablation on single neural processes. On the other hand, in the case of astrocytes was directly damaged, the astrocytic $[Ca^{2+}]_i$ was kept increasing over 10 minutes. The astrocytic $[Ca^{2+}]_i$ increases thus keep long time when astrocytes are damaged seriously. In conclusion, the two-photon laser ablation can sever single neural processes without serious effects on the surrounding astrocytes. By using this laser ablation technique, we are able to cut off an information flow selectively in a neural network, which is useful to study the function of brains, as well as to study neuron-glia interactions after specific cell damages.

Disclosures: **K. Yamaguchi:** None. **R. Kawakami:** None. **T. Nemoto:** None.

Poster

042. Effects of Neuron and Glia Interaction

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Topic: B.12. Glial Mechanisms

Support: Scientia Fellows FP7-PEOPLE-2013-COFUND

Research Council of Norway RCN

Title: Astrocyte Ca2+ signaling in the barrel cortex during active sensation

Authors: *G. B. MELLO, R. A. LANTON, D. M. BJØRNSTAD, W. TANG, E. A. NAGELHUS, K. G. A. VERVAEKE
Univ. of Olso, Oslo, Norway

Abstract: Astrocytes have fine processes in close proximity to neuronal synapses and blood vessels. This has led to the hypothesis that astrocytes may regulate synaptic transmission and couple neural activity to blood flow changes by Ca2+ dependent mechanisms. The evidence for this is however highly controversial. This may be in part due to the wide variety of animal models, tissue preparations, and stimulation protocols that have been used to measure astrocytic Ca2+ changes in response to neuronal activity. Ca2+ changes in astrocytes and the correlated

changes in synaptic transmission and vessel diameter have been observed in intact rodents, but often under anesthesia, and using intense passive sensory stimuli. Thus, there remains a need to monitor Ca2+ changes under more physiological conditions, ideally in well-controlled behavioral paradigms while animals experience behaviorally relevant stimuli. Towards this aim, we performed two-photon Ca2+ imaging with genetically encoded Ca2+ indicators (GCaMP6f) in the barrel cortex of awake head-fixed mice. Ca2+ responses were recorded in mice walking on a treadmill, while in a fraction of trials an obstacle was raised in reach of the whiskers. This allowed us to measure Ca2+ changes during different brain states and in response to sensory stimuli. Importantly, high speed whisker imaging to measure whisker angle and curvature allowed us to qualitatively describe the strength of whisker stimulation. Although locomotion reliably caused Ca2+ increases in the soma, fine processes, and endfeet, whisker touches surprisingly failed to produce detectable Ca2+ changes in any of these compartments. To test whether unphysiologically strong stimuli are able to trigger astrocytic Ca2+ responses, we are currently using optogenetics to stimulate thalamo-cortical projections to the barrel cortex, under both awake and anesthetized conditions. This allows us to titrate the strength of thalamo-cortical input and may provide more information about whether astrocytic Ca+ transients can also derive from sensorial input.

Disclosures: G.B. Mello: None. **R.A. Lanton:** None. **D.M. Bjørnstad:** None. **W. Tang:** None. **E.A. Nagelhus:** None. **K.G.A. Vervaeke:** None.

Poster

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Topic: B.12. Glial Mechanisms

Support: NIH Grant DA035088

Title: Deletion of the astrocytic glutamate release mechanism system x_c^- results in pathological synaptic signaling in nucleus accumbens efferents resulting in perseverative drug seeking

Authors: *E. M. HESS[1], S. KASSEL[1], N. RADDATZ[1], C. MUELLER[1], J. TONG[3], Y. LI[4], Q.-S. LIU[4], A. GEURTS[5], J. R. MANTSCH[1], S. CHOI[2], D. A. BAKER[2]
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Abstract: Glutamate is the primary excitatory neurotransmitter in mammalian brains which renders signaling of this neurotransmitter as a key to understanding CNS activity in normal and diseased states. Identifying pathological changes in glutamate signaling is complicated by the

existence of a complex network of glutamate receptors, transporters, and release mechanisms that are distributed across multiple cell types including astrocytes and neurons. A fundamental question is the potential for pathological glutamate signaling to stem from non-canonical components of the glutamate network. For example, the functional subunit of the astrocytic glutamate release mechanism system x_c^- (Sxc), xCT, is highly conserved across mammalian species suggesting that this protein subserves a critical role in glutamate signaling. Further, xCT expression or Sxc activity is altered in several pathological states or preclinical disease models thought to involve pathological glutamate signaling, such as schizophrenia and addiction. We explored this important question by determining whether the deletion of Sxc activity is sufficient to produce pathological signaling throughout the glutamate network. To do this, we assessed the status of glutamate-related mechanisms expressed by astrocytes, presynaptic neurons, and post-synaptic neurons in transgenic rats lacking functional Sxc (MSxc). In nucleus accumbens astrocytes, we observed decreased uptake of excitatory neurotransmitters in tissue obtained from MSxc rats. In nucleus accumbens post-synaptic neurons, we observed augmented AMPA receptor signaling in striatonigral but not striatopallidal medium spiny neurons. We did not observe evidence of altered presynaptic signaling, which was surprising since Sxc has previously been linked to tonic activation of group 2/3 metabotropic glutamate receptors. Evidence that these molecular changes give rise to pathological glutamate signaling included our observation that MSxc rats displayed enhanced cocaine relapse vulnerability that persevered for days following a cocaine challenge. The nature of this behavior may reflect perseverative responding since MSxc rats display impaired cognitive flexibility measured in a maze-based attentional set-shifting paradigm that was due to an increase in the frequency of perseverative errors. Collectively, these data illustrate the degree to which glutamate signaling involves an integrated network and that pathological synaptic signaling can stem from disruption of non-canonical components of the network such as Sxc.

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Poster

042. Effects of Neuron and Glia Interaction

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Topic: B.12. Glial Mechanisms

Title: Activity-dependent neuronal Klotho production induces astrocytic lactate release through FGFR1 activation and ERK phosphorylation

Authors: *C. MAZUCANTI[1], E. M. KAWAMOTO[2], C. SCAVONE[1], M. P. MATTSON[3], S. CAMANDOLA[4]
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Abstract: Mutations of the β-glucuronidase protein α-Klotho have been associated with aging, but the physiological functions of Klotho and its cellular mechanisms of action are still largely unknown. Klotho is mainly expressed in the kidney where it has been shown to regulate serum phosphate levels. Furthermore, by acting as a hormone through its cleaved and/or secreted form, Klotho is known to partially modulate insulin sensitivity. In addition to the kidney, Klotho is synthesized by neurons. Here we show that cultured hippocampal neurons respond to insulin and glutamate stimulation by elevating Klotho protein levels. Conversely, AMPA and NMDA antagonism negatively affects neuronal Klotho levels. We also show that soluble Klotho enhances astrocytic aerobic glycolysis by hindering mitochondrial pyruvate metabolism and stimulating its processing by lactate dehydrogenase. Pharmacological inhibition of FGFR1, ERK phosphorylation or monocarboxylic acid transporters prevents Klotho-induced lactate release from astrocytes. Neuronal glutamatergic activity and insulin modulation elicit Klotho production, which in turn stimulates astrocytic lactate formation and release; lactate can then be used by neurons as a metabolic substrate to sustain their elevated energy requirements during periods of high excitatory neuronal network activity. Taken together, these data suggest Klotho is a potential new player in the metabolic coupling between neurons and astrocytes.

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Poster

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Topic: B.12. Glial Mechanisms

Support: JSPS KAKENHI 16K08744

Title: Pathological and inflammatory small intestine caused by calcineurin B1 deficiency in glial cells

Authors: *M. TANAKA, M. FUJITA, T. YAGI, U. OKURA, J. TANAKA, N. HIRASHIMA
Nagoya City Univ., Nagoya, Japan

Abstract: *Background & objective:* Calcineurin, also called protein phosphatase 3 (formerly 2B), is a Ca^{2+}/calmodulin-dependent serine/threonine protein phosphatase which is a heterodimer

composed of A (catalytic) and B (regulatory) subunits. It is abundantly expressed in the nervous system and involved in a number of neuronal processes such as neurite extension, synaptic transmission and plasticity, and learning and memory. Although calcineurin is also expressed in glial cells, little is known about roles of calcineurin in glial cells. To investigate the roles of calcineurin in glial cells, we generated glial calcineurin B1-conditional knockout (CKO) mice and analyzed the abnormalities in the CKO mice focusing on the small intestine and the enteric nervous system.
Methods: The CKO mice were generated by crossing floxed calcineurin B1 mice with glial fibrillary acidic protein (GFAP)-Cre mice. To examine the abnormalities in the small intestine of the CKO mice, we performed macroscopic analysis, myeloperoxidase (MPO) assay, histological analysis of cryosections, immunohistochemical analysis of muscle strips with the myenteric plexus, Western blot analysis, and immunocytochemical analysis of stimulated enteric glial cells in culture.
Results: The CKO mice exhibited growth retardation and body weight loss approximately from the third postnatal week. Approximately 80% of the CKO mice died within the fourth postnatal week and the other CKO mice died by postnatal day 75. The small intestine of the CKO mice was thin and yellowish or reddish, and exhibited an increased activity of MPO, an indicator of tissue inflammation. The mucosal layer was degenerated and contained apoptotic cells. GFAP expression was reduced in some areas of the myenteric plexus. However, the density of glia as well as neurons was not reduced but slightly increased in the CKO small intestine. In contrast, no apparent abnormalities were observed in the large intestine of the CKO mice. Nuclear factor of activated T cells failed to translocate into the nucleus after stimulation with ATP in enteric glial cells of the CKO small intestine.
Conclusions: These results suggest that the calcineurin B1 deficiency in enteric glial cells impairs the small intestine and leads to indigestion and/or malabsorption, malnutrition, and eventually death in mice and that calcineurin plays an important role in enteric glial cells. Thus, these CKO mice could be a novel animal model of enteric diseases such as inflammatory bowel disease.

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Poster

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Topic: F.05. Neuroimmunology

Support: CNPq

2016/09364-3, São Paulo Research Foundation (FAPESP)

Title: Central leukotrienes modulate LPS tolerance

Authors: *B. MAITAN SANTOS[1], L. H. ANGENENDT DA COSTA[2], M. J. ALVES DA ROCHA[2], L. G. DE SIQUEIRA BRANCO[2]
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Abstract: Leukotrienes mediate a number of inflammatory events such as neutrophil chemoattraction, leukocyte adhesion, central-releasing of cytokines and fever (the so called a hallmark of inflammation). This study aimed to find out the importance of central leukotrienes in the development of lipopolysaccharide (LPS) tolerance. Thus, we inhibited central leukotriene synthesis in tolerant rats using a pharmacological tool, *i.e.*, a selective inhibitor of leukotriene synthesis MK-886 injected into the third ventricle (3V) of male Wistar rats (270-300 g). Surgical procedures included the placement not only of an intracerebroventricular cannula but also a datalogger into the abdominal cavity, for core body temperature (Tb) measurements. Analgesic (Flunixin; 2.5 mg kg^{-1}, subcutaneously) and antibiotic (160,000 U kg^{-1} benzylpenicillin, intramuscular) drugs were administered before the surgical procedures. After 4 days of recovery, LPS tolerance was induced with a low-dose of LPS (100 µg/kg ip) given for 4 consecutive days. A control group was treated with the vehicle (saline i.p.). During all the experimental period, the animals had free access to water and food and they were kept in a controlled ambient temperature (28-29ºC), which is within the thermoneutral zone. At day 4, rats were microinjected into the 3V with MK-886 immediately before LPS whereas control groups were treated with vehicle (saline). We observed that LPS failed to induce fever after the 3-4 day of treatment, aptly characterizing the tolerance. When MK-886 was given together with saline no change in Tb was observed, but when combined with the forth LPS injection a clear LPS-induced fever was observed. These data are consistent with the notion that central leukotriene is a key molecule to induce LPS tolerance.

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Poster

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Topic: F.05. Neuroimmunology

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Johns Hopkins Medicine Discovery Fund

Title: Role of glutathione S-transferase on astrocyte-microglia communiocations in inflammation

Authors: *E. DOHI, E. CHOI, I. ROSE, T. IMAI, A. SAWA, S.-I. KANO
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Abstract: Astrocytes and microglia play critical roles in brain inflammation, but their functional communications are not fully understood. Here we report unexpected roles for glutathione *S*-transferases (GSTs) enriched in astrocytes, particularly GSTM1 and GSTT2, in astrocyte activation and astrocyte-mediated enhancement of microglia activation during brain inflammation. We found that astrocyte-specific silencing of GSTM1 expression in the prefrontal cortex (PFC) attenuated microglia activation in brain inflammation induced by systemic injection of lipopolysaccharides (LPS). *Gstm1* silencing in astrocytes also attenuated LPS-induced TNF-α production by wild-type microglia in co-culture experiments. In astrocytes, GSTM1 was required for the activation of nuclear factor-κB (NF-κB) and c-Jun N-terminal kinases (JNK) and the production of inflammatory mediators previously implicated in microglia activation, such as chemokine (C-C motif) ligand 2 (CCL2), macrophage colony-stimulating factor (M-CSF/CSF1), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Similar results were also obtained with GSTT2 both *in vitro* and *in vivo* experiments. Thus, our study identified a critical role for astrocytic GSTs in the augmentation of microglia activation in a non-cell autonomous manner during brain inflammation.

Disclosures: E. Dohi: None. **E. Choi:** None. **I. Rose:** None. **T. Imai:** None. **A. Sawa:** None. **S. Kano:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.20/I5

Topic: B.12. Glial Mechanisms

Support: NIH grant P50 MH103222

Title: Systemically applied glutathione or N-acetylcysteine down-regulate endogenous and stimulated kynurenic acid levels in the rat prefrontal cortex

Authors: *R. SCHWARCZ[1,2], H.-Q. WU[2]
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Abstract: The neuromodulatory tryptophan metabolite kynurenic acid (KYNA) is an astrocyte-derived α7 nicotinic and NMDA receptor antagonist, which has been shown to control normal and abnormal cognitive processes in rodents (Schwarcz et al., 2012). In the mammalian brain as elsewhere, KYNA is synthesized from its immediate precursor kynurenine - either by non-enzymatic oxidation or through irreversible enzymatic transamination by kynurenine aminotransferases. Using *in vivo* microdialysis in the prefrontal cortex (PFC) of adult rats, we recently demonstrated that extracellular KYNA levels can be down- and up-regulated, respectively, by focal application of the antioxidant glutathione (GSH) and the GSH synthesis inhibitor L-buthionine sulfoximine (Wu and Schwarcz, SfN, 2016). As these effects caused opposite, secondary changes in extracellular glutamate levels, and as KYNA, GSH and glutamate have all been proposed to participate in the pathophysiology of schizophrenia and other major brain diseases, we suggested that further scrutiny of these events may lead to novel insights regarding the etiology and treatment of these diseases. In present study, we first compared the acute effects of systemically applied GSH (500 mg/kg, ip) with those of N-acetylcysteine (NAC; 500 mg/kg, ip), which boosts GSH content in the brain and has been reported to show clinical efficacy in individuals with schizophrenia (Steullet et al., 2016), on extracellular KYNA in the rat PFC. Both treatments (n=5 each) reliably resulted in a reversible decrease in KYNA levels, with a maximal effect of approx. -25% after 90-120 min and recovery to basal concentrations by 6 hours. Next, we tested the effects of a systemic administration of tryptophan (100 mg/kg, ip; n=5). As expected, extracellular KYNA rose to >300% of baseline levels (maximal effect after 2.5 hours). In separate animals, administration of either GSH (n=3) or NAC (n=5), each injected ip at 500 mg/kg 15 min after tryptophan, reduced the *de novo* production of KYNA from its natural bioprecursor by ~50%. Taken together, these results provide additional evidence for the existence of direct mechanistic links between GSH and brain KYNA, and, more generally, support the idea that KYNA - and by implication astrocytes - may play a relevant role in the effects of systemically supplied antioxidants in brain physiology and pathology.

Disclosures: R. Schwarcz: None. **H. Wu:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.21/I6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF GRFP Fellow #2013161861

Title: The role of astrocyte death in vessel patterning

Authors: *V. M. PUNAL[1], F. S. BRECHA[2], C. YIN[3], M. LEE[2], J. N. KAY[2]
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Abstract: Astrocytes migrate into the developing mouse retina from the optic nerve and proceed to colonize the retinal nerve fiber layer (RNFL) in a centrifugal fashion, a process that begins at E17 and is completed by P5. Developing vasculature mimics this process, with vessel entry into the RNFL temporally offset from astrocyte colonization. There is substantial evidence to suggest that incoming vessels utilize the astrocyte network as a patterning template. Retinal diseases such as retinopathy of prematurity are characterized by defects in vascular patterning. If the ultimate pattern of vessels is determined by a pre-existing astrocyte template, the question naturally arises how astrocytes themselves are patterned. Answering this question will give insight into the mechanisms of normal vascular development, and how it may go wrong in disease. Migration is clearly an important developmental force shaping astrocyte arrangement, and others have investigated the role of astrocyte precursor proliferation. By contrast, relatively little attention has been paid to cell death as an astrocyte patterning mechanism. Here we have investigated the role of developmental cell death in astrocyte and vascular patterning. We find that astrocyte numbers decline by over three-fold during retinal development, an exceedingly large drop by the standards of naturally-occurring neuronal death. We also find that this decline is concurrent with rearrangements in astrocyte soma positioning and morphology. We investigated the mechanisms underlying astrocyte cell death, with the goal of preventing it and learning the consequences for astrocyte and vascular patterning. Our expectation was that astrocyte population size and vessel network density would covary. To this end, we have tested a variety of methods meant to block astrocyte death. We find that there are significant changes to patterning of the astrocyte template and the vessel network when astrocyte numbers are increased. Our future focus is to probe the molecular mechanisms of vessel patterning.

Disclosures: V.M. Punal: None. **F.S. Brecha:** None. **C. Yin:** None. **M. Lee:** None. **J.N. Kay:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.22/I7

Topic: B.12. Glial Mechanisms

Support: FAPESP Grant 14/25927-2

CAPES

Title: P2X7 receptor antagonist is effective in the recovery of enteric glial cells following ischemia and reperfusion

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Abstract: The aim of this study was to analyze the effect of the Brilliant Blue G (BBG, antagonist) on the P2X7 receptor, enteric glial cells (EGCs) and myenteric neurons of the rat ileum following I/R. The ileal vessels were occluded for 45 minutes with an atraumatic vascular clamp. In the I/R 24 h group (n=5), BBG (50 mg/kg) or saline (sal, vehicle, n=5) was given subcutaneous 1 hour after ischemia. In the I/R 14 day and I/R 28 days groups (n=5), BBG was given once daily for the next 5 days following ischemia. Glial cells and myenteric neurons were evaluated for immunoreactivity against the P2X7 receptor, Hu (pan-neuronal), glial fibrillary fibrilar protein (GFAP, glial marker) and S100β (glial marker). Qualitative and quantitative analyses of colocalization, density, profile area were performed via fluorescence and confocal laser scanning microscopy. The myenteric plexus and EGC were analyzed by transmission electron microscopy. The quantitative analyses revealed that a) EGCs and neurons were immunoreactive for P2X7 receptors by 100% in all groups; b) double labelling of S100β/GFAP demonstrated that 29% of the enteric glial cells are immunoreactive only for S100β or GFAP; c) the density of glial cells S100β-IR/cm^2 was increased by 14%, 13% and 12% and, glial cell GFAP-IR was increased by 13%, 38% and 14% in the I/R 24h, 14 days and 28 days groups, respectively; d) the densities of glial S100β-IR and GFAP-IR were decreased by 11%, 11-16% and 10-6% in the BBG 24h, 14 days and 28 days groups, respectively; d) cells P2X7 receptor-IR reduced by 37%, 28% and 24% in the I/R 24h, 14 d and 28 d groups and increased by 21%, 15%, 24% in the BBG 24 h, 14 d and 28d groups; e) neurons Hu-IR reduced by 17%, 18% and 25% in the I/R 24h, 14 d and 28 d groups, respectively and, increased by 6% and 9% in the BBG 14 d and 28d groups, respectively; f) the profile area of Hu-IR neurons was not significantly altered among the groups. The analysis of transmission electron microscopy showed of enteric glial cells close to the neurons. This study showed that the I/R is associated with neuronal loss, increase of glial cells and changes of P2X7 receptor expression. Moreover, it shows that the use of BBG is effective in the recovery of neurons and glial cells and it may be a therapeutic target.

Disclosures: P. Castelucci: None. **C.E. mendes:** None. **K. Palombit:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.23/I8

Topic: B.12. Glial Mechanisms

Support: NIH NS26001

NMSS RG 5053-A-14

Title: Genetic fate-mapping identifies perineurial glia and endoneurial fibroblasts as hedgehog-responsive cell populations in peripheral nerves

Authors: *B. ZOTTER[1], J. SAMANTA[1], H. BALOUI[2], J. L. SALZER[1]
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[2]Departments of Neurosci. and Clin. Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Peripheral nerves contain a variety of cell types in addition to axons and Schwann cells (SCs), including perineurial glia (PG) and endoneurial fibroblast-like cells (EFLCs). Interactions between all of these cellular components are important for proper nerve organization. Thus, PG development is regulated by Desert Hedgehog (Dhh), which is released by SCs. No other known cellular targets and roles of hedgehog signaling during peripheral nerve development have been described.
Here we used a genetic fate-mapping strategy to identify hedgehog-responsive cells in peripheral nerves. Binding of Dhh to its cognate target cells upregulates Gli1, a transcriptional effector of and a read-out for hedgehog signaling. Using this strategy, we have confirmed that PG and, unexpectedly, a population of EFLCs are Gli1 expressing/hedgehog responsive cells. Knockout of Gli1 during development had no obvious effect on PG development but drove a phenotypic switch in EFLCs characterized by reduced extracellular matrix production and extensive minifascicle formation. Minifascicles result from the reorganization of large, peripheral nerve fascicles into multiple, small compartments each invested by their own cellular sheaths. They have been previously reported in Dhh knockouts and following nerve injury, when Dhh expression by SCs is known to decrease significantly. We now propose that EFLCs give rise to minifascicles in response to the reduction in Gli1 signaling that is triggered by loss of Dhh expression - with the latter resulting from disruption of axon-SC interactions. In further support, Gli1-positive EFLCs migrate towards the site of nerve crush and contribute to minifascicle formation following sciatic nerve injury. Taken together, these results suggest that pharmacological manipulation of Dhh signaling by specific targeting of Gli1 may be useful in regulating the EFLC phenotype during nerve repair and regeneration.

Disclosures: B. Zotter: None. **J. Samanta:** None. **H. Baloui:** None. **J.L. Salzer:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.24/DP02/I9 (Dynamic Poster)

Topic: B.12. Glial Mechanisms

Support: ULL GSO 2017

Title: Fibroblast growth factor 1 influences GABAergic interneuron-cortical astrocyte communication

Authors: *D. J. ROGERS[1], M. HENDRICK, 70504[2], M. SIDES[2], K. M. SMITH[3]
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Abstract: Neuron-astrocyte communication is vital to the proper functioning of the central nervous system. Cocultures of GABAergic interneurons grown on *FGFR1*$^{Flox/Flox;HGFAPCre+}$ knock out cortical astrocytes displayed smaller soma size, fewer number of neurites, and a more immature phenotype (K. M. Smith et al., 2014). Changes in neuronal growth may reflect the lack of FGFR1 or may be influenced by dysfunctional neuron-astrocyte communication from impaired astrocytes. FGF2-FGFR1 kinase signaling initiates many intracellular signaling pathways involving cell differentiation, cell proliferation, and calcium signaling, interruption of this pathway may inhibit the effective function of the astrocyte in its communication with GABAergic interneurons. Comparing astrocyte cultures to GABAergic interneurons-astrocyte cocultures using cortical astrocytes from *FGFR1*$^{Flox/Flox;NestinCre+}$ and control p2-4 mice, calcium imaging of physiological responses were studied. Genotype had no effect on number of spontaneous calcium waves, duration or intensity in either the astrocyte cultures or the GABAergic interneuron-astrocyte coculture. 25µM Glutamate increased calcium signaling in control (p=.0038) and *FGFR1*$^{Flox/Flox;NestinCre+}$ cortical astrocyte cultures (p=.0038). 25µM Glutamate stimulation of control cocultures, revealed no increase in astrocyte calcium signaling in contrast to the significantly increased signaling by astrocytes without interneurons. 25µM Glutamate stimulation of *FGFR1*$^{Flox/Flox;NestinCre+}$ cortical astrocyte in coculture decreased calcium signaling significantly more that the control coculture astrocyte (p=.0347). The decreased signaling in response to 25µM Glutamate in astrocytes may be due to GABA signaling from the interneurons. This will be confirmed through testing with GABA and the GABAergic antagonist, Bicuculline.

Disclosures: D.J. Rogers: None. **M. Hendrick:** None. **M. Sides:** None. **K.M. Smith:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.25/I10

Topic: B.12. Glial Mechanisms

Support: NSF CAREER AWARD 1149446

Title: Neuronal hyaluronan mediates the dimensions of brain extracellular space in the naked mole-rat

Authors: *D. THEVALINGAM[1,2], N. LAMASSA[1], G. PHILLIPS[2,1], D. P. MCCLOSKEY[2,1]
[1]Col. of Staten Island, Staten Island, NY; [2]City Univ. of New York, Staten Island, NY

Abstract: Hyaluronan (HA) is a linear glycosaminoglycan (GAG) that is a primary component in the extracellular matrix within the nervous system. As a critical structural component in the extracellular matrix of the brain, soluble HA content markedly enhances amount of extracellular space available in the brain. Previous work has shown that tissues in the African Naked Mole-Rat, including brain, accumulate an exceptionally high amount of HA, likely due to decreased activity of digestion enzymes, which confers early contact inhibition and cancer resistance in this species [Tian et al. (2013) Nature. 499(7458): 346–349]. The purpose of this present study is to explore how the presence of HA affects the dimensions of extracellular space within the naked mole-rat hippocampus. Hippocampal sections from the CA3 region were processed and fixed for transmission electron microscopy imaging. Samples were either treated with a bacterial hyaluronidase (75 units/ml) or ACSF vehicle for 5 minutes in an experimenter-blind fashion. Subsequent image analysis demonstrated that the digestion of HA with hyaluronidase resulted in a significant decrease in the area of the extracellular space, as well as a reduction in the synaptic cleft widths. Extracellular space widths were obtained by manual measurements and the average ECS width calculated for Group A: 16.29 nm ± 2.17 nm; for Group B: 22.42 nm ± 3.08 nm; two-tailed two-sample homoscedastic t-test: $p<0.05$). The identity of samples were confirmed after analysis, Group A received hyaluronidase treatment and Group B received control treatment. We propose that HA serves an enhanced role in this species to facilitate the rapid diffusion of molecules and the substances in the brain in order to counteract the extreme conditions of the naked mole-rat microenvironment.

Disclosures: D. Thevalingam: None. **N. Lamassa:** None. **G. Phillips:** None. **D.P. McCloskey:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.26/J1

Topic: F.05. Neuroimmunology

Support: PAPIIT IG200314

Consejo Nacional de Ciencia y Tecnología 220598

Title: Rapid activation of the sensory autonomic nervous system mediated by prostaglandins in acute LPS challange

Authors: *E. SANTACRUZ[1], E. SOTO-TINOCO[2], R. M. BUIJS[2]
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Abstract: Upon inflammatory stimuli, the innate immune system is regularly suppressed by signals coming from the autonomic nervous system. For this to happen the nervous system first needs to be informed that there is an immune challenge. Currently, it is accepted that this is done through cytokines, which are proteins secreted by the immune system, nevertheless, the nervous system shows signs of activation before these proteins can be secreted, and thus sensed. For this reason, a non protein mediator is probably responsible for this early activation. Prostaglandins are known to be immune lipidic mediators that are secreted prior to cytokines, and which nociceptive neuronal terminals are capable of sensing LPS. We hypothesized that prostaglandins are the first immune mediator to be sensed by the autonomic nervous system. To investigate this, we inhibited prostaglandin synthesis by indomethacin administration in LPS challenged male Wistar rats. Neuronal activation of the sensory elements is assessed by c-Fos expression in the dorsal horn (DH) of the spinal cord as well as the nucleus of the solitary tract (NTS) fifty minutes after the LPS challenge to avoid cytokine induced neuronal activation. Systemic prostaglandin synthesis inhibition, nevertheless, doesn't give information about the anatomical localization for prostaglandin sensing since circumventricular organs as well as free nervous terminals have the capacity to sense prostaglandins. To assess this problem indomethacin was administered i.c.v. to inhibit prostaglandin synthesis in circumventricular organs in LPS treated rats. In conclusion the early activation of the DH and the NTS is due to sensing of prostaglandin in the periphery.

Disclosures: E. Santacruz: None. **E. Soto-Tinoco:** None. **R.M. Buijs:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.27/J2

Topic: B.12. Glial Mechanisms

Title: L-Lactate and Glycine interact synergistically to potentiate NMDA receptor activity : A form of metapotentiation?

Authors: *P. J. MAGISTRETTI[1,2], P. JOURDAIN[3], I. ALLAMAN[4], P. MARQUET[5], K. ROTHENFUSSER[6]
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Abstract: *N*-methyl-d-aspartate (NMDA) receptors are a family of glutamate receptors requiring two distinct molecules to be active: glutamate as the main agonist and glycine (or D-Serine) as a potentiator. In addition, recent studies have demonstrated that L-Lactate, released from astrocytes, can also act as modulator of neuronal plasticity and Long-Term memory formation (Suzuki *et al.*, 2011). This effect is mediated by a positive modulatory action of lactate on NMDA receptors (Yang *et al.*, 2014). Here we have studied the potential synergy between these three molecules to potentiate NMDA receptor activity. To this end, we performed Ca^{2+} imaging using Fura-2 to measure $[Ca^{2+}]_i$ elevations in cultured neurons during and after glutamate stimulation. We observed that a pulse of glutamate at a low concentration (1μM; 2min) triggered a small and transient increase of $[Ca^{2+}]_i$ with a maximum peak height of 0.24 +/- 0.03 u.a. (n_{cult} = 9; n_{cells} = 432) which did not change significantly in the presence of 10 mM of L-Lactate (0.27 +/- 0.03 u.a; p = 0.20). Co-application of glutamate (1μM) and glycine (100μM) however produced a Ca^{2+} response with a strong increase in maximum peak height in presence of L-Lactate (0.22 +/- 0.03 u.a. *vs* 0.36 +/- 0.03 u.a.; $p < 0.001$; n_{cult} = 11; n_{cells} = 468). This indicates the requirement of both glutamate and glycine for the L-Lactate-induced potentiation of the $[Ca^{2+}]_i$ response. Interestingly, neither D-Lactate (10mM) nor Pyruvate (10mM) were able to potentiate the $[Ca^{2+}]_i$ response induced by co-application of glutamate/glycine, confirming the specificity of L-Lactate. This potentiation of Ca^{2+} response by L-Lactate disappeared in the presence of higher concentrations of glutamate (10 to 100μM), suggesting a booster function of L-Lactate limited to subliminar activation of the NMDA receptor.

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Poster

042. Effects of Neuron and Glia Interaction

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Topic: B.12. Glial Mechanisms

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Title: Chemokine CCL2-CCR2 signaling induces neuronal cell death via STAT3 activation and IL-1β production after status epilepticus

Authors: *J. PENG[1,2], D. TIAN[3,4], M. MURUGAN[4], J.-L. LIU[3], U. B. EYO[5], W. WANG[3], L.-J. WU[6,2]
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Abstract: Elevated levels of chemokine C-C motif ligand 2 (CCL2) and its receptor CCR2 have been reported in patients with temporal lobe epilepsy and in experimental seizures. However, the functional significance and molecular mechanism underlying CCL2-CCR2 signaling in epileptic brain remains largely unknown. In this study, we used kainic acid-(KA) induced seizure model to examine the CCL2-CCR2 signaling pathways. KA (0.15 μg in 5 μl ACSF) was infused to one side of the lateral ventricle (ICV) of the awake mice via a pre-implanted cannula. The acute seizure responses were scored for 2 hr and EEG monitoring was done at the same time and continued for 2 weeks to detect any recurrent seizures. We found that both CCR2 KO ($CCR2^{RFP/RFP}$) and CCL2 KO mice showed similar severity and duration of acute seizure responses as WT mice. However, the seizure induced neuronal damages, which mainly occurred in the CA3 area of the ipsilateral hippocampus shown with Fluro Jade B (FJB) staining, were dramatically reduced in both CCR2 KO and CCL2 KO mice. The upregulated CCL2 was mainly expressed in hippocampal neurons and activated microglia from mice 1d after KA-induced seizures, while CCR2 was seen only in the blood-derived monocytes. Taking advantage of $CX3CR1^{GFP/+}$:$CCR2^{RFP/+}$ double transgenic mice, we demonstrated that CCL2-CCR2 signaling participated in resident microglial activation and blood-derived monocyte infiltration. We further showed that CCR2 activation induced STAT3 phosphorylation and IL-1β production, which are critical for promoting neuronal cell death after status epilepticus. Consistently, pharmacological inhibition of STAT3 by WP1066 reduced seizure-induced IL-1β production and subsequent neuronal death. Two weeks after KA-induced seizures, CCR2 deficiency not only reduced neuronal loss, but also attenuated seizure-induced behavioral impairments, including anxiety, memory decline, and KA induced recurrent seizure severity. Taken together, we demonstrated that CCL2-CCR2 signaling contributes to neurodegeneration via STAT3 activation and IL-1β production after status epilepticus, providing potential therapeutic targets for the treatment of epilepsy.

Disclosures: J. Peng: None. **D. Tian:** None. **M. Murugan:** None. **J. Liu:** None. **U.B. Eyo:** None. **W. Wang:** None. **L. Wu:** None.

Poster

042. Effects of Neuron and Glia Interaction

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 042.29/J4

Topic: B.12. Glial Mechanisms

Support: NIH RO1 HL128454 (DDK)

Title: Excitatory amino acid transporters (EAATs) modulate nTS synaptic and neuronal properties; role of metabotropic glutamate receptors (mGluRs)

Authors: *D. MARTINEZ, D. D. KLINE
Biomed. Sciences/Dalton Cardiovasc. Res. Ctr., Univ. of Missouri, Columbia, MO

Abstract: The nucleus tractus solitarii (nTS) is the central integration site for visceral afferent reflexes including baroreflex control of blood pressure. Sensory afferent signals are transmitted to brainstem nTS neurons via release of the excitatory neurotransmitter glutamate (Glu). Astrocytic excitatory amino acid transporters (EAATs) in the nTS are critical to maintaining extracellular Glu concentration, and thus profoundly modulate synaptic signaling and neuronal activity. Our previous studies have shown that block of EAATs with the general antagonist DL-threo-β-Benzyloxyaspartic acid (DL-TBOA) depolarize nTS neurons and increase the frequency of spontaneous excitatory postsynaptic currents (sEPSCs). Contrary to the effects on sEPSCs, EAAT block reduced the amplitude of afferent (TS)-driven EPSCs. The goal of this study is to determine the mechanism(s) by which this differential effect on EPSCs may occur. Group II and III metabotropic Glu receptors (mGluRs II / III) are localized in sensory afferents and their activation decreases TS-EPSC amplitude. Therefore, we hypothesize that elevated Glu following EAAT block with TBOA activates mGluR II / III on the sensory afferent terminals, which inhibits TS-EPSCs. Brainstem nTS slices were generated from Sprague-Dawley rats, and sEPSCs, TS-EPSCs, holding currents (I_{hold}), and membrane potential (V_m) were recorded from monosynaptic nTS neurons. Electrophysiological properties were examined during EAAT block with TBOA alone, and subsequently during dual block of EAAT and mGluR II / III (TBOA with mGluR II / III antagonists EGLU and MSOP). Bath application of TBOA induced depolarization of the membrane, as shown by changes in V_m and induction of inward I_{hold} when held at -60mV. However, in the presence of mGluR II / III blockade the magnitude of depolarization was comparable to TBOA alone. TS-stimulation evoked EPSCs were significantly decreased following EAAT block, and mGluR II / III antagonism did not prevent TBOA-induced attenuation, although this response was variable. Inhibition of EAATs significantly and reversibly increased the frequency of sEPSCs, indicative of an increase in nTS network activity. In contrast to other parameters, mGluR II / III block attenuated the TBOA-induced increase in sEPSC frequency. The amplitude of the sEPSCs was not altered in TBOA or TBOA in the presence of mGluR II / III antagonist. Together, these data suggest a differential role of mGluR II / III on modulating afferent driven and spontaneous EPSCs during elevation of extracellular glutamate, and suggest an important role of EAATs in this modulation.

Disclosures: D. Martinez: None. **D.D. Kline:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Topic: B.12. Glial Mechanisms

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Holland Trice Brain Research

Foerster-Bernstein

Hartwell Foundation

Title: Astrocytic neuroligins control astrocyte neuropil infiltration and synaptic connectivity

Authors: *J. A. STOGSDILL[1], J. RAMIREZ[1], Y.-H. KIM[2], D. LIU[2], K. T. BALDWIN[1], E. ENUSTUN[1], T. EJIKEME[1], R.-R. JI[2], C. EROGLU[1]
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Abstract: Astrocytes are morphologically complex cells of the brain that perform critical central nervous system functions. Fine cellular processes of astrocytes penetrate the neuropil, thereby maintaining synaptic homeostasis and modulate synapse numbers and strength. The cellular and molecular mechanisms that control neuropil infiltration and overall cellular morphogenesis of astrocytes is lacking. Furthermore, it is unclear how the morphological development of astrocytes affects synaptic connectivity. Here, we uncover that cortical astrocyte morphogenesis is dependent on direct contact with neuronal processes. Unexpectedly, astrocyte morphology and neuropil infiltration is dependent upon the expression of the neuroligin (NL) family of cell adhesion proteins NL1, NL2, and NL3 within astrocytes. Transcellular interactions between astrocytic NLs and their well-known neuronal binding partner neurexins (Nrx) regulate the morphology of astrocytes. To gain insight into the link between astrocyte neuropil infiltration and synaptic connectivity, we deleted NL2 specifically in astrocytes and quantified synapse numbers and measured synaptic function. Surprisingly, deletion of NL2 in cortical astrocytes impairs excitatory synaptic connectivity, while inhibitory synaptic function is enhanced. Our findings uncover a novel mechanism of action of NLs in astrocytes and reveal a connection between astrocyte morphology and synapse formation. Loss-of-function mutations in NLs, including NL2 are implicated in human cognitive disorders such as autism and schizophrenia.

Therefore, understanding the distinct roles of these cell adhesion molecules in astrocytes and neurons is fundamental to unraveling their mechanisms of neural pathology.

Disclosures: J.A. Stogsdill: None. **J. Ramirez:** None. **Y. Kim:** None. **D. Liu:** None. **K.T. Baldwin:** None. **E. Enustun:** None. **T. Ejikeme:** None. **R. Ji:** None. **C. Eroglu:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 043.02/J6

Topic: B.12. Glial Mechanisms

Support: R01MH100822 to CMA

Title: Lactate from astrocytes: A major energy source for the learning-induced translation required for long-term memory formation

Authors: *G. DESCALZI, V. GAO, M. Q. STEINMAN, C. M. ALBERINI
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Abstract: Although significant progress has been made regarding the neuronal mechanisms underlying learning and memory, much less is known about the contribution of neuroglia. It is well established that the formation of long-term memory requires *de novo* protein synthesis in neurons, and numerous neuronal transcripts have been identified whose translation is critical for long-term memory formation. Protein synthesis requires a large amount of energy, and several studies indicate astrocytic lactate as an efficient energy substrate for neurons. Lactate is produced by aerobic glycolysis in astrocytes and shuttled into neurons. We have previously shown that, in rats, inhibitory avoidance (IA) learning leads to release of lactate into the extracellular space in the hippocampus, and pharmacological inhibition of hippocampal glycogenolysis with DAB blocks lactate release and long-term memory. The memory impairment is rescued by hippocampal injection of lactate, but not by equicaloric concentration of glucose. Here we asked: what is the role of lactate? We found that blockade of astrocytic breakdown of glycogen into lactate or downregulation of the expression of glia monocarboxylate transporters (MCT) 1 and 4, which disrupt memory formation, can be rescued by either pyruvate or the ketone body B3HB. Downregulation of the neuronal monocarboxylate transporter MCT2 prevented the rescuing effects of either pyruvate or B3HB, suggesting that a critical role of lactate is to supply energy for neuronal functions. In addition, *in vivo* surface sensing of translation (SUnSET) revealed that hippocampal injection of DAB prevents the increase in *de novo* learning-induced translation, which, however, is rescued by lactate. We thus conclude that the role of lactate is to provide critical metabolic support to mediate learning-induced translation necessary for long-term memory formation.

Disclosures: **G. Descalzi:** None. **V. Gao:** None. **M.Q. Steinman:** None. **C.M. Alberini:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: B.12. Glial Mechanisms

Support: NIH R01NS079166

NIH R01DA036165

McLaughlin Fellowship from UTMB

Title: The activation of glial cells contributes to HIV-1-gp120- induce synapse degeneration

Authors: ***W. RU**, S.-J. TANG
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Abstract: Human immunodeficiency virus (HIV) infection induces neuronal injuries, with almost 50% of infected individuals developing HIV-associated neurocognitive disorders (HAND). Although highly activate antiretroviral therapy (HAART) has significantly reduced the incidence of sever dementia, the overall prevalence of HAND remains high. Synapse degeneration emerges as one of the most relevant neuropathologies associate with HAND. Previous studies indicate critical roles of viral proteins and inflammatory responses in the pathogenesis. As HIV-1 cannot infect neurons, HIV-associated synapse degeneration is likely a bystander effect of the infected cells, including macrophages, microglia and astrocytes. However, the mechanism(s) by which glial cells contributes to HIV-1- associated synaptic degeneration is unclear. Recently, new findings provide the evidence that glial cells actively communicate with neurons and modulate synapse elimination and plasticity through an array of secreted and contact-dependent signals. We propose that disruption in neuron-glia signaling contributes to HIV-1-related synaptic degeneration and cognitive impairment. Firstly, we have determined the effects of HIV-1 coat protein gp120 on neuronal synapses in primary cortical cultures and the mouse frontal cortex. Using western blotting analysis, we detected decrease of pre- and post-synaptic makers following gp120 exposure. Moreover, confocal imaging also revealed the decreased synapses puncta in the gp120Tg mice cortices. Interestingly, we found that gp120 caused microglia and astrocytes activation that was concomitant with the decrease of synaptic proteins. Blockage of microglial activation abolished the gp120-induced synapse loss in the cortical cultures. In addition, we also observed that fractalkine, a chemokine that is specifically expressed in neurons and can regulate microglia activation, was up-regulated in gp120-treated primary cortical cultures. These results indicate that fractalkine-mediated

microglial activation may involve in gp120-induced synapse loss. We are currently testing the potential role of the reactive astrocytes in synapse degeneration and the interaction of microglia and astrocytes in HAND pathogenesis.

Disclosures: W. Ru: None. **S. Tang:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Topic: B.12. Glial Mechanisms

Support: NIH Grant F31NS089178

NIH Grant R01NS078294

McNair Medical Institute

Title: Local calcium-dependent astrocyte signaling modulates primary olfactory neuron activity

Authors: *K. UNG[1], B. R. ARENKIEL[2]
[1]Developmental Biol., [2]Mol. & Human Genetis and Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Elucidating the cellular and molecular mechanisms of how neurons form synapses and establish patterns of connectivity is required to gain needed insight into circuit formation and function in the developing, aging, and diseased brain. Knowledge of such mechanisms may lead to the development of new circuit repair-based therapies for replacing damaged or diseased nervous tissue. Astrocytes comprise a prominent glial cell type in the CNS, and have been identified to contribute towards proper synaptic maintenance and function. Moreover, defective astrocytes have been associated with several neurological disease states, such as Alzheimer's, schizophrenia, epilepsy, tumorigenesis, and autism spectrum disorder. Taking into account the known functional roles of astrocytes, along with our preliminary data, we are currently testing the hypothesis that: *local astrocytes play essential roles in neuronal circuit processing.* Exploiting the anatomy and experimental tractability of the mouse olfactory system, here we aim to manipulate astrocyte activity, and examine the effects on olfactory bulb circuit processing. Towards this, we genetically targeted astrocytes to utilize pharmacogenetic manipulations for *in vivo* widefield imaging and electrophysiological approaches. We found that astrocytes exhibit an odor-response sensory map that overlaps with pyramidal neurons. We also found that manipulating astrocyte activity affects olfactory-stimulated neuronal responses *in vivo* and spontaneous neuronal activity *ex vivo*, suggesting that astrocytes play an active role in processing olfactory circuits. Behavioral experiments show that these astrocyte activity manipulations affect

neuronal olfactory circuit processes. Together our evolving data support a functional and critical role for astrocytes in normal neuronal circuit function. Uncovering novel functional roles for astrocytes toward circuit function may not only better inform us of brain development and function, but also may help explain how defects in astrocytes contribute to neurodegenerative diseases.

Disclosures: K. Ung: None. **B.R. Arenkiel:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 043.05/J9

Topic: B.12. Glial Mechanisms

Support: NSERC 195814317

Title: Astrocytes are common effectors of corticosterone- and serotonin-mediated alteration of cortical inhibition

Authors: *C. A. WOTTON, E. F. QUON, L. K. BEKAR
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Abstract: Corticosterone (CORT) and serotonin (5-HT) are both known to mediate changes in cortical inhibition to shape network activity. As single astrocytes 1) communicate with over 100,000 synapses, 2) can influence inhibitory interneuron activity through established purinergic mechanisms, and 3) have the ability to influence whole networks via regulation of extracellular potassium (directly affects neuron excitability), we assessed a possible astrocytic involvement in CORT and 5HT-mediated alteration of cortical inhibition.
METHODS: We used a paired-pulse stimulation paradigm and extracellular field recordings in mouse cortical brain slices to assess alterations in sensory adaptation/suppression that has previously been shown to be $GABA_A$-receptor dependent.
RESULTS: Under normal conditions, both 5HT and CORT decrease the amplitude of the first evoked potential (P1) while increasing the second (P2), for a large increase in the paired-pulse ratio (P2/P1) which is consistent with a decrease in adaptation/suppression. The typical increase in P2 is reversed in the presence of the $GABA_A$-receptor antagonist bicuculline, now showing a decrease, confirming a role of cortical inhibition in the 5-HT and CORT effects on cortical paired-pulse suppression.
To assess the astrocytic role in these changes, we pre-treated cortical slices with iodoacetate before assessing CORT and 5-HT effects. Similar to bicuculline, iodoacetate disrupted 5-HT and CORT effects on P2, now also showing a decrease instead of an increase. To examine the role of purinergic signaling we used the P2Y receptor antagonist Ab129 in the presence of both CORT

and 5-HT. P2Y receptors appear to play a larger role in CORT mediated alterations as the CORT response on both P1 and P2 was fully blocked with Ab129 whereas only the response on P2 was affected in response to 5HT.
CONCLUSIONS: These results suggest CORT and 5-HT affect cortical inhibition through modulation of astrocytic purinergic networks. Although both 5HT and CORT appear to recruit astrocytes and $GABA_A$-receptors, the signaling pathways differ. Astrocytic dysregulation is increasingly recognized to occur in psychiatric disorders. This may be related to chronic glucocorticoid and/or altered serotonin signaling that is also characteristic of these conditions.

Disclosures: C.A. Wotton: None. **E.F. Quon:** None. **L.K. Bekar:** None.

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

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NSF 1557971

Title: Microglial contributions to network remodeling in adult ocular dominance plasticity

Authors: *M. S. MENDES[1], A. K. MAJEWSKA[2]
[1]Neurosci., Univ. of Rochester, Rochester, NY; [2]Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Microglia are the brain resident macrophages and the first line of defense in the event of disease. In the healthy brain, microglia make contacts with neurons at synapses, influence synaptic remodeling and maintain neuronal circuits. Recent work has shown that microglia are critical contributors to an experience-dependent plasticity that occurs in the visual cortex during the visual critical period, which in mice corresponds to a period of early adolescence. During this period, monocular deprivation (MD) of the contralateral eye results in a reduction of the cortical response to vision through this eye and is termed ocular dominance plasticity (ODP) because of the resulting shift in the cortical responsiveness towards the non-deprived eye. It has been suggested that this reduction results, in part, from the phagocytosis of synapses carrying information from the deprived eye by cortical microglia. While it is generally accepted that the adult primary visual cortex (V1) is less plastic, experience-dependent plasticity can be induced in adult V1 but relies on different mechanisms. Although, both developmental and adult ODP

depend on N-methyl –D- aspartate (NMDA) receptor activation, adult ODP is much slower and involves the potentiation of the non-deprived eye response without a depression of the response mediated by the deprived eye. The contribution of microglia to adult ODP has not been explored. To determine whether microglia contribute to adult ODP, we depleted microglia from the brain using the colony stimulating factor 1 (CSFR1) inhibitor PLX5622. This inhibitor has been demonstrated to deplete microglia in mice by 80% after 1 week of treatment. C57BL/6J mice (~2-month-old) were fed PLX5622 (1200 ppm in chow) for 21-30 days, while controls received normal chow. The duration of deprivation has a profound effect on the extent of cortical changes. In adult mice, five-day MD was sufficient to induce a robust shift in the cortical preference for the non-deprived eye. This deprivation-induced change in ocular dominance was assessed using intrinsic optic signal (iOS) imaging. Mice treated with PLX5622 for 21-30 days and maintained on PLX5622 during MD showed normal ocular dominance shifts after 5 days of MD, demonstrating that pharmacological depletion of microglia has no effect on adult ODP and that microglia are unlikely to play an important role in this form of adult plasticity. We are now in the process of investigating whether microglial depletion affects ODP in critical period mice. These experiments will contribute to our understanding of the roles of microglia during different types of plasticity.

Disclosures: **M.S. Mendes:** None. **A.K. Majewska:** None.

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: NIH Grant R01-DA031833

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Title: How do astrocyte-secreted thrombospondins and their neuronal receptor alpha-2-delta-1 shape cortical connectivity?

Authors: *W. C. RISHER[1], N. KIM[2], E. F. SPENCE[3], P. R. MITEV[4], L.-J. PILAZ[5], D. WANG[7], G. FENG[7], D. L. SILVER[6], S. H. SODERLING[1], H. H. YIN[2], C. EROGLU[1]
[1]Cell Biol. / Neurobio., [2]Psychology and Neurosci., [3]Cell Biol., [4]Neurobio., [5]Mol. Genet. &

Microbiology, [6]Mol. Genet. & Microbiology / Neurobio., Duke Univ. Med. Ctr., Durham, NC; [7]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Astrocytes, the most abundant cell type in the brain, have been identified as key regulators of synaptogenesis. Astrocytes secrete thrombospondin family proteins (TSPs) that strongly induce excitatory synapse formation between cultured retinal ganglion cells (RGCs). TSPs bind to and act through their neuronal receptor, the calcium channel subunit, alpha-2-delta-1 (α2δ-1). However, the mechanism by which this interaction results in synapse formation, as well as the requirement for α2δ-1 for synaptic connectivity in the developing cortex, is unknown. Using null and conditional mouse alleles of α2δ-1, we found that α2δ-1 is required for the proper establishment of cortical synapses. Global loss of one or both alleles of the α2δ-1 gene results in profound deficits in dendritic outgrowth, synapse numbers, and synaptic activity. Furthermore, ultrastructural examination of dendrites by three-dimensional serial section electron microscopy revealed that loss of α2δ-1 severely altered spine morphology, revealing the importance of this protein for numerous stages of neuronal development. Though α2δ-1 is expressed by neurons both pre- and postsynaptically, we determined that postsynaptic α2δ-1 is both necessary and sufficient to regulate synaptic development both *in vitro* and *in vivo*. Finally, we have shown that Rac1, a key promoter of the actin cytoskeleton in spines, acts downstream of TSP/α2δ-1 to induce cortical synapse and spine formation and maturation.
In summary, our results show that astrocytes promote synapse and spine maturation via secreted TSP acting on neuronal α2δ-1 to regulate synaptic connectivity and morphology in the developing cortex.

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Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: NIH R21MH104280

NIH R01MH106553

Title: Activation of neonatal microglia can be influenced by other neural cells

Authors: *A. TURANO, J. H. LAWRENCE, J. M. SCHWARZ
Univ. of Delaware, Newark, DE

Abstract: During development, microglial progenitor cells migrate into the brain from the periphery: a process critical to the maturation of the developing brain. Although they perform functions similar to mature, adult microglia, immature microglia are distinct from mature microglia. Activation of immature microglia, via an immune challenge, can lead to persistent changes in microglial function, which results in long-term neuronal and cognitive dysfunction. Early-life immune activation is associated with multiple neurodevelopmental disorders including autism, ADHD, schizophrenia, and cerebral palsy - disorders with suspected immune etiologies, as well as strong sex biases for males. Still, immature microglial activation requires further characterization to determine its potential role in these neurodevelopmental disorders. More work is also necessary to better understand the relationship between immature microglia and other developing neural cells during this critical period of development. Based on human epidemiological data and rat models of immune activation, we hypothesized that microglia isolated from male rat pups would be more vulnerable to an immune challenge during early development than female microglia. We also predicted that other neural cells would influence immature microglial activation. We exposed freshly-isolated, sex-specific, microglial cells from the hippocampus of rat pups to lipopolysaccharide on P4, in the presence or absence of other neural cells. Mixed and microglial cultures were analyzed for inflammatory gene expression to determine whether immature microglia exhibited a sex-specific response to immune activation, and if the presence of all other neural cells influenced that response. We found that the microglial response to an LPS immune activation differed depending on the presence or absence of all other neural cells within the culture. While we found very few sex differences in the immune response, we did observe that the microglial expression of IL-6, following immune activation, was more robust in male microglia that were in the presence of all other neural cells than female microglia in the same environment.

Disclosures: A. Turano: None. **J.H. Lawrence:** None. **J.M. Schwarz:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: B.12. Glial Mechanisms

Support: Intramural Research Program of NINDS

Title: Neuron-glia interactions in the *Drosophila* larval visual system

Authors: *M. E. GIBBS, Q. YUAN
Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD

Abstract: Glia perform important functions within the nervous system, and defective neuron-glia interactions have been implicated in numerous neurological diseases. To study the role of neuron-glia interactions in neuronal development and synaptogenesis, we utilized ventral lateral neurons (LNvs) in the *Drosophila* larval visual system as a model. Glia in the *Drosophila* central nervous system (CNS) have been categorized into three distinct types: surface glia, cortex glia, and astrocytes. We performed a dual-labeling screen using fourteen glia GAL4 enhancer trap lines. Three lines with expression patterns in cortex glia and astrocytes were found to be in close physical proximity to LNvs, providing a genetic handle for us to manipulate specific glia types and detect changes in LNv function and structure. We performed synaptobrevin GFP Reconstitution Across Synaptic Partners (GRASP) to visualize and validate physical interactions between CNS glia and LNvs. One half of a split GFP fragment was expressed in glia and the other half of the split GFP fragment was targeted to LNv membrane. The reconstituted GFP signals indicate the precise locations where glia and LNvs physically contact. Using this technique, we found that cortex glia wraps LNv axons and cell bodies, while astrocyte processes intermingle with LNv axons and dendrites. Furthermore, previous research indicates that fluctuations in glial intracellular calcium influence neuronal processes. We expressed parvalbumin (PV), which sequesters intracellular calcium, in astrocytes and observed significant reductions in LNv dendrite volume, suggesting that modifying intracellular calcium signaling in astrocytes influences LNv dendrite morphogenesis. Based on the anatomical and functional connections between glia and LNvs that we found in this study, we are planning genetic screens to identify glial genes involved in neuron-glia interactions that play a role in regulating neuronal development and synaptogenesis.

Disclosures: M.E. Gibbs: None. **Q. Yuan:** None.

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: R21 MH107029-01A1

R01 HD067218-05

Title: *In vivo* Ca^{2+} signaling in astrocytes in awake behaving mice

Authors: *P. RAGUNATHAN, A. DUNAEVSKY
Developmental Neurosci., Munroe-Meyer Institute, Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Astrocytes display activity-mediated Ca^{2+} responses and Ca^{2+} signaling in astrocytes is thought to be involved in astrocyte-neuron signaling. In order to understand how astrocytes are engaged during different behaviors in vivo, we performed in vivo imaging in the primary motor cortex (M1) of awake head-fixed mice engaged in different behaviors in a mobile home cage. Synchronized video recordings and electromyogram recordings during the time-lapse volume imaging sessions were performed in mice that express the genetically encoded Ca^{2+} indicator GCaMP6f in astrocytes. Ca^{2+} activity acquired in a 20-50 micron thick volume over a 5 minute imaging period is analyzed. The patterns of Ca^{2+} activity exhibited in the astrocyte somatic and process compartments associated with different behaviors (quiet resting versus running periods) as well as whether movement promotes synchronous increases in Ca^{2+} activity are examined. Studying Ca^{2+} signaling that occurs in the different compartments including microdomains is necessary to understand how astrocytes contribute to brain function. Although several studies have shown that motor-skill learning induces changes in synaptic structure and function, whether these synaptic changes are accompanied with learning induced changes in astrocytic Ca^{2+} signaling has not been studied. Repeated in vivo imaging was performed over days to monitor the time course of changes in astrocytic Ca^{2+} signaling with learning and to understand its relationship to learning induced changes in dendritic spines.

Disclosures: P. Ragunathan: None. **A. Dunaevsky:** None.

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: BBSRC Grant BB/M021793/1

Title: Mapping synapses and astrocytic processes in the mammalian spinal cord

Authors: *M. J. BROADHEAD[1,2], F. ZHU[3], L. ARCINAS[1], S. G. N. GRANT[3], G. B. MILES[1]
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Abstract: The spinal cord contains the neural circuitry necessary for the generation of movements such as locomotion, as well as sensation and pain detection. Anatomically different neural circuits may show structurally and molecularly distinct synaptic features that could also vary over development and ageing. In addition, astrocytes in the central nervous system, which associate with synapses via fine dendritic processes, may contribute to this synaptic diversity. Large scale mapping of both synapses and astrocytes together could therefore provide a more

detailed understanding of the factors affecting synaptic physiology within distinct neural circuits of the spinal cord. In this study, we have used a genetically engineered mouse expressing fluorescently labelled PSD-95 and quantitative microscopy methods to map excitatory synapses and astrocytes in the spinal cord. From large scale image analysis of synapses, we show inter-regional and age dependent diversity in excitatory synapse structure and molecular composition. We further used super-resolution microscopy to interrogate the structural differences between synapses of different spinal cord circuits, namely dorsal and ventral horn synapses. Combining synapse analysis with immunohistochemistry staining of astrocytes, we show the degree of synapse association with astrocytes varies between ages. Furthermore, synapses found with astrocytes are structurally larger and molecularly more enriched with PSD-95 than synapses without astrocytic contact. The nature of this interaction between astrocytes and synapses varied between sub-regions of the spinal cord, and between different age groups. Our data provides a thorough baseline understanding of excitatory synapse diversity in the spinal cord, providing insights into the functional differences between sensory, integrational, and motor circuits. Furthermore, we have applied a highly quantitative microscopy approach to study the relationship between synapses and astrocytes. We show that synapses are structurally and molecular enriched when contacted by astrocytes, and the nature of this interaction changes between ages and between different neural circuitry.

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Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: NIH R15NS095314

NSF-MRI DBI0821211

Title: Neuronal plasticity and survival in spinal cord following peripheral axon injury: Role of glia

Authors: *J. MALONEY, ***J. MALONEY**, R. SNYDER, N. D. HENKEL, J. M. HUTCHINSON, L. G. ISAACSON
Ctr. for Neurosci. and Behavior, Dept. of Biol., Miami Univ., Oxford, OH

Abstract: Previously we reported that transection of distal axons in the cervical sympathetic trunk (CST) leads to robust retrograde neuronal and glial plasticity in the upper thoracic spinal

cord. One week following injury the parent sympathetic preganglionic neurons housed in the intermediolateral cell column (IML) exhibit transient plasticity, including decreased expression of choline acetyltransferase (ChAT) and exclusive expression of activating transcription factor 3 (ATF3). The injured preganglionic neurons also release injury signals that activate nearby microglia, astrocytes, and oligodendrocyte (OL) lineage cells in the IML. Because glial cells secrete cytokines that signal to surrounding cells we hypothesized that the glial plasticity observed at one week post-injury contributes to the long-term survival of the injured IML neurons. In the present study, we administered the antibiotic minocycline to dampen microglial activation and assessed the role of glial activation on neuronal plasticity and survival following CST transection. Starting on the day of surgery Sprague Dawley rats received daily ip injections of minocycline (Mino; 50mg/kg for 2 days; 25mg/kg for 5 days; n=10) or vehicle (VEH; saline; 2ml/kg; n=10) for one week following bilateral CST transection (n=12) or sham (n=8) surgery. A second group of rats received similar treatment but was examined four months following surgery. At one week post-injury, microglia in the IML of Mino rats exhibited a reduced activation state, with significantly fewer amoeboid microglia (no processes) and significantly more quiescent microglia (3-4 primary processes). The dampening of microglia activation with Mino also resulted in a significantly reduced number of astrocytes and OLs in the IML of injured animals. In addition to the reduction of glial activation with Mino, a reversal in the typical decrease in ChAT expression was observed with significantly more IML neurons expressing ChAT. ATF3 expression in the injured neurons remained unchanged. Four months post-injury, fewer ChAT neurons were present in the IML of the injured Mino group, suggesting that dampening glial activation and reduced neurotransmitter plasticity by the injured neurons during the first week following injury contributed to long-term neuronal loss. We conclude that activated glial cells present near the injured IML cell bodies following CST transection contribute to neurotransmitter plasticity in the injured neurons as well as to their long-term survival. These results provide evidence of beneficial crosstalk between spinal cord glial cells and neurons following distal axonal injury, possibly to promote neuronal survival.

Disclosures: **J. Maloney:** None. **R. Snyder:** None. **N.D. Henkel:** None. **J.M. Hutchinson:** None. **L.G. Isaacson:** None.

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: NIH R15NS095314

NSF-MRI DBI0821211

Title: Elimination of microglia from mouse spinal cord: A model to examine plasticity following peripheral axon injury

Authors: *J. HUTCHINSON[1,2], J. MALONEY[2], N. D. HENKEL[2], L. G. ISAACSON[2]
[2]Ctr. for Neurosci. and Behavior, Dept. of Biol., [1]Miami Univ., Oxford, OH

Abstract: Previous studies in our lab have shown that the transection of preganglionic axons of the cervical sympathetic trunk (CST) results in a robust activation of glial cells within the intermediolateral cell column (IML) of the spinal cord near the injured neuronal cell bodies. This transient increase in the number of glial cells results by way of retrograde signals from the injury site. One week following CST transection, activated microglia are observed within the IML, characterized by increased expression of ionized calcium-binding adapter (Iba1), cellular aggregation, and amoeboid-like morphology. Increased numbers of oligodendrocyte (OL) lineage cells are also observed. Because there is evidence for glial crosstalk, i.e. microglia-derived cytokines signaling to OLs, we aimed to block microglia in the mouse spinal cord to investigate their role in the OL lineage cell plasticity typically observed following CST transection. Young adult C57BL/6 mice were fed a diet containing PLX5622 (n=12), a colony stimulating factor-1 receptor (CSF1R) inhibitor shown to eliminate microglia in the central nervous system, or a control diet (n=12), for a total of 28 days. On day 21 of the diet, half of each diet group underwent either bilateral CST transection (Inj+PLX, n=6; Inj+Control, n=6) or sham surgery (Sham+PLX, n=6; Sham+Control, n=6). The mice then remained on the PLX5622 or control diet for an additional 7 days following injury in order to assess any changes to typical glial plasticity. In the PLX5562 mice, microglia were nearly eliminated in spinal cord: the number of microglia was reduced in IML of sham mice and injury PLX mice by 76% and 91%, respectively, compared to their control diet counterparts. Notably, the activated microglia present in the IML of the Inj+Control mice were completely absent in the IML of Inj+PLX mice. Yet, neuronal expression of the injury marker activating transcription factor 3 (ATF3) in IML was not different between Inj+PLX and Inj+Control mice. These findings indicate that the PLX diet dramatically reduced the number of microglia in the spinal cord and blocked the increase in activated microglia typically observed following injury. In addition, we conclude that activated microglia do not play a role in the expression of ATF3 by injured neurons. Our results establish an approach to investigate the role microglia play in OL plasticity as well as in the coordinated response to injury previously observed in our lab.

Disclosures: J. Hutchinson: None. **J. Maloney:** None. **N.D. Henkel:** None. **L.G. Isaacson:** None.

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: NIH R15NS095314

NSF-MRI DBI0821211

Title: Glial proliferation in rat and mouse spinal cord in response to peripheral axon injury

Authors: *L. G. ISAACSON, N. D. HENKEL, L. J. SCHNEIDER, D. SULLIVAN, A. KOLLIAS, J. MALONEY, J. M. HUTCHINSON
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Abstract: In previous studies we have shown that transection of the distal cervical sympathetic trunk (CST) results in glial plasticity in the intermediolateral cell column (IML) of the rat and mouse spinal cord, a response that results from the release of retrograde injury signals by the injured neurons. At one week following CST transection, this response is characterized by a significant increase in the number of activated microglia as well as increased numbers of oligodendrocyte (OL) lineage cells near the injured neuronal cell bodies. The objective of this study was to determine whether the increase in glial cells in the IML observed following CST transection was the result of glial proliferation and whether any proliferation was followed by differentiation/survival. Young adult Sprague Dawley rats or C57BL/6 mice received daily injections of BrdU (rats) or EdU (mice) for 7 days following CST transection and thoracic spinal cords (both the IML and adjacent white matter) were examined for proliferation at one week following injury. A second group of rats was examined at 8 weeks following the last BrdU injection. BrdU and EdU cells showed respective increases of 3-fold and 24-fold in the IML at one week following injury, compared with shams, indicating that robust proliferation in the spinal cord occurred in response to distal axon injury. In both rat and mouse, significant increases in microglia and OL precursor cell (OPC) proliferation were observed compared with shams. The majority of the proliferating cells observed in the IML at one week post-injury were microglia, with approximately 68% and 90% of the proliferating cells, respectively, co-localizing Iba1, a marker for microglia. Approximately 10% of the EdU cells in the IML co-localized NG2, a marker for OPCs. At 8 weeks post-injury, the total number of BrdU cells was decreased by 50% compared to 1 week, indicating that many of the proliferating cells did not survive. While the proportion of the proliferating cells that were microglia at 8 weeks was significantly reduced by 35% compared to 1 week, a trend toward an increase in the proportion of BrdU cells colabeled with CC1, a marker for mature OLs, was observed. The results of this study reveal that distal peripheral injury can elicit a robust proliferation of glial cells in the rat and mouse spinal cord. Most of the proliferating cells were microglia, while only a minor proportion were OL lineage cells. We conclude that injured neurons in the IML release factors into the microenvironment to stimulate glial proliferation, although many of the microglia did not survive. However, our data suggest that the newly formed OPCs may survive and differentiate into mature OLs.

Disclosures: L.G. Isaacson: None. **N.D. Henkel:** None. **L.J. Schneider:** None. **D. Sullivan:** None. **A. Kollias:** None. **J. Maloney:** None. **J.M. Hutchinson:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 043.15/K7

Topic: B.12. Glial Mechanisms

Support: JSPS KAKENHI 16H01329

JSPS KAKENHI 17H03988

JSPS KAKENHI 17H05738

Title: Microglia trim dentate synapses during development

Authors: *Y. KASAHARA, H. UEDA, R. KOYAMA, Y. IKEGAYA
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Abstract: In the adult dentate gyrus, the granule cells project the mossy fiber axons to the stratum lucidum of hippocampal CA3, forming synapses on CA3 pyramidal cells. However, the development of mossy fiber pathways is not fully clarified. Here, we immunohistochemically assessed the developmental distribution of synaptoporin (SPO), a protein that is present in mossy fiber boutons, in the postnatal mouse hippocampus. We found a bundle of punctate SPO signals in the inner molecular layer of the dentate gyrus as well as the stratum lucidum in postnatal-3-day-old (P3) mice. Ectopic SPO signals in the inner molecular layer weakened gradually and disappeared by P60. Next, we investigated the possible involvement of microglia, the brain-resident immune cells, in the disappearance of SPO signals, because microglia engulf inappropriate or unnecessary synapses via their phagocytic capacity. Suppression of microglial activation by treatment with minocycline increased the intensity of SPO signals in the inner molecular layer without affecting the SPO signal intensity in the stratum lucidum. Thus, our findings suggest that granule cells project their axons to the molecular layer in early postnatal periods and form synapses therein, which are removed by microglia during juvenile periods.

Disclosures: **Y. Kasahara:** None. **H. Ueda:** None. **R. Koyama:** None. **Y. Ikegaya:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Topic: B.12. Glial Mechanisms

Support: European Union Seventh Framework Programme (FP7) under grant agreement No. 604102 (HBP)

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Academy of Finland (decision No. 297893)

Title: Astrocyte-modulated synaptic plasticity in sensory cortex in health and pathology: A computational study

Authors: A. SAUDARGIENE[1], T. MANNINEN[2], R. HAVELA[2], *M.-L. LINNE[2]
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Abstract: Astrocytes have been shown to exhibit dynamic transients in intracellular calcium concentration *in vitro* (Cornell-Bell et al. 1990) and *in vivo* in awake behaving mice (Ding et al. 2014). Moreover, astrocyte processes are intimately associated with brain synapses and, according to a very recent evidence, express fast calcium transients (Panatier et al. 2011, Kanemaru et al. 2014). These transients in processes differ from those in the soma in terms of frequency, kinetics, and spatial spread, and may be governed by separate signaling mechanisms compared to soma. We develop a new computational model for astrocyte-neuron interactions and signaling pathways in a developing somatosensory cortex to test *in silico* the capacity of astrocyte processes to sense ongoing neural activity and modulate synapses both in health and in pathologies. The model describes major biophysical and biochemical mechanisms in one-compartmental presynaptic neuron terminal, two-compartmental postsynaptic neuron, and a one-compartmental astrocytic process. We apply classical pre- and postsynaptic stimulation protocols for long-term plasticity as synaptic inputs to activate the model. Presynaptic stimulation triggers glutamate release and activates AMPA receptors and metabotropic glutamate receptors (mGluRs) on dendritic membrane of the postsynaptic cell. Postsynaptic stimulation, induced by somatic current injection, triggers a somatic action potential that propagates back into the dendritic compartment and opens voltage-sensitive calcium channels. Calcium influx into a postsynaptic cell together with the glutamate-activated mGluRs triggers a cascade of biochemical reactions that activates phospholipase C. This leads to diacylglycerol production and 2-arachidonoylglycerol endocannabinoid release. Endocannabinoids bind to the cannabinoid receptors on the astrocyte membrane and initiate a signaling cascade which activates inositol

1,4,5-trisphosphate receptors (IP3Rs). IP3Rs are responsible for calcium release from the endoplasmic reticulum to the cytosol which leads to the elevated calcium levels in the cytosol of the astrocyte. Elevated astrocytic calcium level can induce calcium-dependent release of gliotransmitters from the astrocyte to modulate the vesicle release in the presynaptic terminal. Our hypothesis is that increased intracellular calcium concentration in astrocytes plays an important role in synaptic plasticity and learning. The long-term goal of our work is to develop extended synapse models, including other mechanisms possibly contributing to plasticity in sensory cortex in normal and pathological conditions.

Disclosures: A. Saudargiene: None. **T. Manninen:** None. **R. Havela:** None. **M. Linne:** None.

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: NIH Grant R01 NS088627

NIH Grant R21 DE025689

New Jersey Commission for Spinal Cord Injury Research CSCR15ERG015

Title: Microglia process convergence in swell-like conditions is modulated by neuronal activity and purinergic signaling

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Abstract: Cerebral edema or swelling of the brain tissue, can occur as a result of traumatic, as well as, non-traumatic events such as epilepsy and stroke. One of the common features of edema is the swelling of cells, which is caused by the accumulation of excess extracellular fluid. During edema, swelling of neurons and glial cells such as astrocytes in the central nervous system (CNS) have been reported. However, the response of microglia, the key immune cells in the CNS, in edema-like conditions remains uninvestigated. In the present study, we explore the response of microglia to neuronal swelling. Using a combination of time-lapse two-photon imaging and whole-cell patch clamp recordings, the interaction between microglia and neurons was studied in live brain slices obtained from mice (P18-25). Three models of swelling, including (1) swelling of entire tissue by hypotonic bath application, (2) single neuron swelling by replacing with hyper-tonic intracellular solution and (3) single neuron swelling induced by neuronal firing, were used. In all three models, neuronal swelling was accompanied by increased occurrence of microglial processes convergence (MPC) at random focal points. The MPC events were

abolished in mice lacking purinergic receptor P2Y12R, suggesting the involvement of purinergic signaling. Moreover, sodium channel blocker (tetrodotoxin- TTX) and NMDAR antagonist (AP5) were able to reduce the occurrence of MPC events in response to single neuron swelling. This suggests that microglia make physical contact with neurons in response to neuronal excitability. However, the exact relevance of this phenomena remains unclear and is under investigation. The characterization of this phenomenon in swell-like conditions is key to understanding the nature and function of these microglial events in the context of cerebral edema.

Disclosures: M. Murugan: None. **L. Wu:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Topic: B.12. Glial Mechanisms

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Neurosciences Training Grant T32 NS067431

Title: Loss of the neurodegenerative-disease associated microglial receptor, Trem2, extends the period of complement-mediated synaptic pruning in development

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Abstract: Microglia play essential roles in shaping the brain in development, in part through refining synaptic connections through complement-mediated synaptic pruning. Recent work suggests that these developmental functions of microglia are aberrantly re-initiated in the context of neurodegenerative diseases, contributing to disease-associated synaptic loss. Variants in the gene encoding the microglial receptor Trem2 confer risk for multiple neurodegenerative diseases, demonstrating a clear role for Trem2 in disease-related microglial functions. However, the mechanisms linking Trem2 variants to disease are still unclear. In order to determine whether

Trem2 contributes to disease progression through altering development-associated synaptic pruning mechanisms, we examined changes in the complement system and synapses in mice lacking Trem2 expression throughout normal development, between 1 and 8 months of age. We found that Trem2 deficiency altered microglial morphology and gene expression at all ages examined. At 4 months of age, these changes in microglial function resulted in enhanced astrocytosis. In order to determine whether these changes in microglial and astrocytic phenotypes correlated with altered complement levels, we examined changes in RNA and protein levels of complement components and their receptors. In brain lysates from Trem2 deficient mice, we found trends toward increased levels of complement protein levels at 1 month of age which were significantly elevated by 4 months. These differences were largely normalized by 8 months of age. In line with these changes in complement proteins, we found small but significant reductions in some postsynaptic components in Trem2 deficient mice at 1 month of age. By 4 months of age, there were more dramatic reductions in protein levels of postsynaptic markers. Gene expression of postsynaptic markers were unchanged, suggesting that this was not transcriptionally regulated. These findings are consistent with altered microglial-mediated synaptic elimination. Levels of postsynaptic proteins were no longer significantly altered at 8 months of age, suggesting a possible late compensatory mechanism that normalizes astrocyte reactivity, complement protein expression and ultimately synapse number. Together, our findings suggest that Trem2 plays an important role in regulating microglial-mediated synaptic elimination following the typical period of developmental synaptic refinement.

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Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Topic: B.12. Glial Mechanisms

Support: Regeneration Next Postdoctoral Fellowship

NIH F32 EY027997

Title: Müller glia-secreted thrombospondin family proteins regulate retinal synapse development

Authors: *S. KOH[1,2], J. KAY[3,4], C. EROGLU[1,2,3,4]
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Abstract: Neural retina is a CNS structure composed of well-organized layers of neurons with distinct functions. The neuroanatomy and circuit-specific synaptic organization of the retina have

been extensively studied and a number of neuronal molecular pathways that regulate synaptic connectivity in the retina have been identified; however, neuron-glia interactions that drive synaptic development in the retina are still not understood. Here we studied the requirements of Müller glia (MG)-secreted Thrombospondins (TSP), TSP1 and TSP2, in establishing retinal synaptic connectivity. Using RNA-fluorescence in situ hybridization (RNA-FISH) combined with immunohistochemistry (IHC), we found that MG produce TSP1 and TSP2 in the retina. TSP1 and TSP2 were enriched within the synaptic outer and inner plexiform layers (OPL and IPL, respectively), and their common synaptogenic neuronal receptor, α2δ-1, is also enriched at both synaptic layers. To determine the requirement of TSP/α2δ-1 signaling in retinal synapse development, we utilized transgenic mice that lack α2δ-1 (α2δ-1 KO) or TSP1 (TSP1 KO) or TSP2 (TSP2 KO). Our findings reveal that TSPs and their receptor α2δ-1 are critical for formation of retinal excitatory synapses. Interestingly, we found that TSP1 and TSP2 perform non-overlapping roles in regulating retinal synaptic connectivity, indicating that TSP-signaling modulates circuit-specific retinal synapse development.

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Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Topic: B.12. Glial Mechanisms

Support: NIH Grant R01AG041944

Title: Aging exacerbates immune challenge triggered activation of hippocampal microglia in a rodent model of delirium

Authors: *A. S. ARNOLD, C. R. FITZGERALD, N. SALLA, N. TANAKA, S. L. PATTERSON
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Abstract: Aging increases the risk of an abrupt cognitive decline, sometimes called delirium, following an injury or illness. Little is known about why aging brains are more vulnerable, however, research has shown that the immune and central nervous systems communicate extensively. Data from rodent models suggest microglia, cells of the innate immune system, become primed (sensitized) to respond to signals from the peripheral immune system and other parts of the brain with age. Fischer Brown Norway (F344xBN) rats display little to no physical or cognitive impairment at 24 months. However, in response to a single intraperitoneal injection of E. coli, microglial production of proinflammatory cytokines is potentiated and prolonged in the aged (24 months) rats compared to production in their younger (3 months) counterparts. We

have previously demonstrated that these aged animals have deficits in hippocampus-dependent long-term memory and memory-related synaptic plasticity that mirror the elevations in proinflammatory cytokines. We are now more closely examining the aging-associated dysregulation of microglia within the hippocampus. In addition to producing proinflammatory cytokines, activated microglia act as phagocytes, cleaning up detritus and stripping synapses from dead and damaged neurons. We are using immunohistochemistry for IBA1, a microglial membrane protein, to compare microglial numbers, distribution and morphological changes triggered by a peripheral immune challenge in old and young animals with or without a recent history of E. coli infection. Preliminary findings indicate that there are more activated microglia in the infected vs. saline groups and in the aged vs. young groups. We will also be looking at IBA1 expression at different time points after infection to investigate how long the microglia remain activated in the different groups.The increased activation of microglial cells within hippocampal tissue of aged-infected rats is consistent with the idea that the dysregulation of the immune system may play a significant role in an abrupt cognitive decline and possibly in progression to dementia.

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Poster

043. Role of Glia in Synapse Formation and Function

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Topic: B.12. Glial Mechanisms

Support: NIH Grant NS057499

Title: Store-operated calcium channels in astrocytes play a key role in regulating thrombin-induced excitability of hippocampal CA1 neurons

Authors: *K. HORI, A. B. TOTH, M. PRAKRIYA
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Abstract: Store-operated Ca^{2+} release-activated Ca^{2+} (CRAC) channels are a major pathway for calcium signaling in many cells and serve numerous functions, including gene expression, the production release of cytokines, and cell motility. However, their role in the brain is not well understood. Astrocytes are critical cell type in the brain, and are implicated in a diverse range of functions including metabolic support, regulation of extracellular ion balance, and regulation of synaptic communication. Unlike neurons whose function is dictated by the firing of action potentials, effector functions in astrocytes are driven exclusively by elevations in intracellular calcium. Recent evidence indicates that CRAC channels are a major mechanism for driving

elevations in $[Ca^{2+}]_i$ and triggering the release of gliotransmitters, which would be expected to influence the activity of neighboring neurons. Here, we investigated the contributions of astrocyte CRAC channels for regulating synaptic communication in the hippocampus. Because astrocytes, but not neurons, express protease activated receptors (PAR), PAR agonists, such as thrombin, can stimulate only astrocytes. Using astrocyte-specific knockout mice of Orai1, the protein encoding the channel pore ($Orai1^{fl/fl}$ GFAP-CRE), we tested the effect of thrombin in CA1 pyramidal neurons. Administration of thrombin to hippocampal slices caused a burst of spontaneous IPSCs (sIPSCs) on CA1 pyramidal neurons. This thrombin-induced IPSC burst was abolished in $Orai1^{fl/fl}$ GFAP-CRE mice, indicating that activation of PAR receptors on astrocytes causes stimulation of CA1 interneurons. In the presence of TTX, thrombin did not affect the frequencies of miniature IPSCs (mIPSCs), indicating that the increase of sIPSC frequency results through an action potential-dependent mechanism in interneurons. Amplitudes of the sIPSCs and mIPSCs were unchanged by thrombin. These results indicate an important role for store-operated CRAC channels in astrocytes for the modulation of hippocampal interneuron activity and pyramidal neuron excitability.

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Poster

043. Role of Glia in Synapse Formation and Function

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Program#/Poster#: 043.22/L2

Topic: F.05. Neuroimmunology

Support: Knut and Alice Wallenberg's Foundation 20140212

Heart Lung Foundation 20150767

Title: Electrical vagus nerve stimulation accelerates resolution of inflammation in experimental peritonitis

Authors: *A. S. CARAVACA, L. TARNAWSKI, H. ARNARDOTTIR, M. BÄCK, P. S. OLOFSSON
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Abstract: The vagus nerve is an integral component of the inflammatory reflex, a neural reflex mechanism that regulates cytokine production at the onset of inflammation. It was recently shown that zymosan-induced peritoneal inflammation was increased, and resolution prolonged in vagotomized mice (Mirakaj, *et al*. J. Exp. Med., 2014). It is not clear whether electrical stimulation of the vagus nerve can regulate resolution of inflammation. In light of this, we subjected C56BL/6 mice to electrical vagus nerve stimulation (VNS) by delivering a 300μA

current (250 μs biphasic pulse, 50 μs interphase delay, 10 Hz) for 60 seconds or sham stimulation to the left cervical vagus nerve using bipolar hook electrodes. Twelve hours after stimulation, mice were injected intraperitoneally with zymosan, a TLR2 agonist, to induce inflammation. Peritoneal exudates were collected at 4, 12, 24, 48 hours after injection and neutrophils were quantified by light microscopy and flow cytometry. The resolution interval (R_i) (defined by Bannenberg, *et al*. J. Immunol., 2005) was ~18 hours in the sham group versus ~12 hours in the VNS group, i.e. ~32% reduced in VNS treated animals. Macrophage clearance of apoptotic neutrophils (efferocytosis), a key process of resolution, was increased in the VNS group compared to the sham group as assessed by flow cytometry. In mice lacking the alpha-7 nicotinic acetylcholine receptor subunit, VNS did not reduce the R_i or increase efferocytosis. Furthermore, human macrophages exposed to acetylcholine in the presence or absence of zymosan showed increased levels of maresin 1, a mediator of resolution, as measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). These results indicate that VNS reduces R_i and increases efferocytosis in zymosan-induced peritonitis through a mechanism that requires the nicotinic acetylcholine receptor alpha-7 subunit and possibly cholinergic activation of maresin 1 biosynthesis. Further experiments are warranted to define the mechanisms and molecular therapeutic targets in neural control of inflammation resolution.

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Poster

043. Role of Glia in Synapse Formation and Function

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Topic: F.05. Neuroimmunology

Support: NHMRC Fellowship 1117079

NHMRC Fellowship 1072878

NIH NIAAA Grant R24AA017225

Title: Antibodies in the brain of people with schizophrenia and controls

Authors: *L. J. GLASS[1], D. SINCLAIR, 2204[2], D. BOERRIGTER[3], K. NAUDE[3], S. J. FUNG[4], D. BROWN[6], V. S. CATTS[5], P. TOONEY[7], M. O'DONNELL[8], R. LENROOT[4], C. GALLETLY[10], D. LIU[10], T. W. WEICKERT[9], C. S. WEICKERT[4]
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Australia; [7]Sch. of Med. Sci. and Pharm., Univ. of Newcastle, Newcastle, Australia; [8]Sch. of Psychiatry, Univ. of New South Wales, Sydney, Australia; [9]Univ. of New South Wales, Randwick, Australia; [10]Adelaide Univ., Adelaide, Australia

Abstract: Background The immune system is implicated in schizophrenia pathology as ~40% of patient brains have elevated proinflammatory cytokine mRNA. Despite schizophrenia symptomology present in some autoimmune diseases, antibodies (specifically IgG) have not been explored in the schizophrenia brain. We investigated the following 1) the presence and localisation of IgG in the prefrontal cortex (PFC) of humans and rhesus macaques, 2) the abundance of IgG, and its transporter (Fc neonatal receptor; FcGRT) protein and mRNA in the PFC of people with schizophrenia compared to healthy controls and the impact of elevated pro-inflammatory cytokines, and 3) the presence and abundance of brain-reactive IgG (BR-IgG) in the plasma of living schizophrenia patients and healthy controls.Methods and ResultsIgG presence was detected surrounding blood vessels in the post mortem (PM) orbitofrontal cortex of schizophrenia cases (n=38) and controls (n=38), and the PM rhesus macaque prefrontal cortex (PFC; n=7) using immunohistochemistry. We quantified IgG and FcGRT protein, and FcGRT mRNA in the human PM dorsolateral PFC with Western blot and qPCR respectively. There were no significant differences (all $p>0.05$) in all measurements when comparing schizophrenia (n=37) with controls (n=37), high inflammation individuals (n=18) with low inflammation individuals (n=56), and people with schizophrenia in a high inflammation state (n=14), people with schizophrenia in a low inflammation state (n=23), with controls in a low inflammation state (n=33. Indirect immunofluorescence showed that plasma BR-IgG bound to monkey cerebellar tissue in six distinctive patterns including molecular layer punctate cellular with bright Purkinje neurons (10%, 17/166) and fibrous staining throughout the tissue (14%, 23/166). The incidence of plasma with a BR-IgG positive signal was comparable between plasma from schizophrenia patients (n=94) and that of controls (n=72; $\chi 2=0.5$, $p=0.479$). However, when using pixel intensity to quantify BR-IgG levels schizophrenia patient plasma contained less BR-IgG that control plasma [$t(164)=-2.463$, $p=0.015$]. ConclusionsWe have shown IgG is present in both the normal human brain and schizophrenia brain. However, plasma BR-IgG is decreased in living schizophrenia patients. As recent work has found that IgG can act as an immunomodulatory, this indicates that reduced IgG in the blood may be detrimental in consequences in schizophrenia.

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Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Program#/Poster#: 043.24/L4

Topic: F.05. Neuroimmunology

Support: CIHR Grant MOP-123372

Title: Impact of immune function on mouse brain morphology

Authors: *S. SPRING[1], C. CORRE[1], A. TU[1], L. R. QIU[1], D. A. VOUSDEN[1], J. A. FOSTER[2], M. R. PALMERT[1], J. P. LERCH[1]
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Abstract: The discovery of lymphatic vasculature in the central nervous system suggests a close interaction between the brain and the systemic immune system (1). To study how the peripheral immune system modifies the brain, we used 3D magnetic resonance imaging (MRI) to assess the brain morphometry of 11 mutant mouse strains each deficient in one element of the immune system including Cxcr2, CD4, CD8, Ighm, IL-10, IL-18, IL-6, Kit, Nos2, Rag1, and Rag2. Fifteen male and 15 female mice from each of the 11 strains along with wild-type controls were studied. A multi-channel 7.0-T MRI scanner with a 40 cm diameter bore (Varian Inc., Palo Alto, CA) was used to acquire anatomical images of brains within skulls (2). The brain images of all animals were aligned using a previously described automated image registration pipeline generating deformation fields relating each individual image to the consensus study average (3). Deformation data was used to calculate brain structure volumes and localized changes on an individual voxel level. All changes are reported as normalized data to whole brain volume. Minimal changes to brain morphology were seen in relative brain structure volume and voxel-wise comparisons in mice lacking the chemokine receptor Cxcr2, nitric oxide-generating enzyme Nos2 and adaptive immune system components Rag1, Rag2, Ighm and CD8. Strains lacking cytokines IL-10 and IL-6 both showed growth in regions of the cerebellar cortex and hippocampus. Regions of the pons, anterior commissure, cortex and olfactory bulbs were also larger in the IL-10 knockout strains but regions of the thalamus, cortex, amygdala and striatum were smaller in this strain compared to controls. The CD4 knockout mutant showed growth in regions of the cerebellum, the periaqueductal grey (PAG) region, hypothalamus, hippocampus, corpus callosum and striatum but had smaller olfactory bulbs compared to controls. The most dramatic changes to neuroanatomy were seen in the IL-18 and Kit knockout mouse strains. The IL-18 strain showed significant growth in the cerebellum and other smaller regions throughout the brain along with a reduction in size of regions in the hippocampus, cortex, amygdala and hypothalamus. The Kit mutant strain demonstrated growth in the cerebellar cortex, medulla and PAG but significant regions of size reduction in the cortex, thalamus, hypothalamus and olfactory bulbs were also observed.
Together our data indicate that the immune system has widespread effects on brain development and that a broad range of structures are affected which together warrant further study.
1. Louveau et al. (2015) Nature
2. Lerch et al. (2011) Methods Mol Biol
3. Lerch et al. (2008). NeuroImage

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

Poster

043. Role of Glia in Synapse Formation and Function

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Topic: F.05. Neuroimmunology

Title: The effect of LPS and minocycline administration on small-molecule plasma and brain metabolites

Authors: *S. CHAN[1], F. PROBERT[2], J. SWANN[3], D. C. ANTHONY[2], P. W. J. BURNET[1]
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Abstract: Introduction: Given the strong association between pro-inflammatory cytokines and psychiatric disorders, drugs with anti-inflammatory properties, such as minocycline, have gained interest as possible therapeutic agents. However, the mechanisms underlying their psychotropic properties are unclear. In this study, we investigated the effect of lipopolysaccharide (LPS) and minocycline on brain and plasma metabolites using metabolomics.Methods: Male CD1 mice received repeated (7days) intraperitoneal injections of minocycline (50ug/kg) or saline. On the 7^{th} day, animals received an injection of LPS or saline, and plasma and brain tissue were collected 24 hours later. Plasma samples were diluted in phosphate buffer (75mM, D_2O), and NMR spectra obtained on a Bruker AVIII 700MHz spectrometer, and processed with MestreNova. Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to determine differences in the metabolic profiles between treatment groups. Tissue samples were extracted in perchloric acid, and lipid pellets were further extracted in dichloromethane. Mass spectrometry was used to identify the lipid-phase metabolites. Results: OPLS-DA modelling separated the LPS-alone (Sal/LPS) animals from control (Sal/Sal) in plasma. The model generated was able to predict if a test sample belonged to the Sal/Sal or Sal/LPS group with 97% accuracy. A similar result was obtained for the minocycline-treated animals, with the model differentiating between the minocycline-alone (Mino/Sal) and the minocycline and LPS-treated (Mino/LPS) animals with 84.5% accuracy. However, the model generated between the Sal/LPS and Mino/LPS groups was also significantly more accurate than a randomly generated model (+16.7% Accuracy, $p<0.05$), suggesting that Mino/LPS and Sal/LPS may form different clusters. As the important variables involved in building these models are peaks associated with lipoproteins, a second study involving lipid-phase metabolites and mass spectrometry will be conducted with brain tissue. Preliminary analyses has shown that we are able to detect most of the major lipid classes with our extraction protocol. We predict that the different treatment

groups will form different clusters. Conclusion: We have previously shown aqueous brain metabolite changes following a single peripheral LPS injection. In this study, we show that plasma metabolite changes after LPS injection is linked to lipid-associated peaks. Studying the metabolome in both plasma and brain tissue will allow a better understanding of pathways that are affected by LPS and minocycline.

Disclosures: S. Chan: None. **F. Probert:** None. **J. Swann:** None. **D.C. Anthony:** None. **P.W.J. Burnet:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 043.26/L6

Topic: F.05. Neuroimmunology

Support: NIH Grant GM0709077

NIH Grant AI117911

Title: Neuronal basis of the adrenergic receptor OCTR-1 in regulating the innate immune response of *Caenorhabditis elegans*

Authors: *X. CAO, A. ABALLAY
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Abstract: Increasing evidence from studies in neurobiology and immunology implies an extensive and universal interaction between the nervous and immune systems, which is responsible for organismal control of immune homeostasis. In contrast to the complexity of mammalian systems, the simple model organism *C. elegans* has been validated as a powerful tool to study host-pathogen interactions and investigate the principles of neural regulation of immunity. Previous studies in our laboratory have shown that OCTR-1, a neuronal G protein-coupled receptor (GPCR) analogous to human norepinephrine receptors, functions in two sensory neurons, ASH and ASI to control the gene expressions of both the microbial killing pathways and the unfolded protein response (UPR) in *C. elegans*. To examine the precise molecular and neuronal mechanism of the regulation of pathogen defenses, we performed the targeted ablation of each neurons and found that OCTR-1-expressing neurons, ASH, are involved in controlling the resistance to pathogen infections. In contrast, another group of OCTR-1-expressing neurons, ASI, were shown to promote pathogen avoidance behavior. Through the analysis of the previous microarray data, we were able to identify a neuropeptide gene, *nlp-20* that is upregulated in *octr-1(ok371)* mutant and functions downstream of OCTR-1 to control the innate immune response in *C. elegans*. In addition, interneurons AIA were found to

modulate immune response and function as a putative linker between OCTR-1-expressing and NLP-20-expressing neurons. Taken together, these data reveal the downstream molecules that are responsible for OCTR-1-mediated immune regulation and provide new insights into the neuronal network involved in regulating the pathogen defense response in *C. elegans*.

Disclosures: X. Cao: None. **A. Aballay:** None.

Poster

043. Role of Glia in Synapse Formation and Function

Location: Halls A-C

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Program#/Poster#: 043.27/L7

Topic: F.05. Neuroimmunology

Support: NIH P30 NSO69375 06

NIH R21 NS097945 01

Title: Beta1 adrenergic receptors modulate systemic and central inflammation in an acute *In vivo* model of lipopolysaccharide challenge

Authors: *A. K. EVANS[1], B. YI[2], J. ERNEST[2], M. SHAMLOO[2]
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Abstract: Severe degeneration of Locus Coeruleus noradrenergic (NA) neurons has been reported in Alzheimer's Disease (AD), and loss of noradrenergic tone may contribute not only to cognitive dysfunction, but also to neuroinflammation and underlying disease progression. Specifically, beta adrenergic receptors (adrb1 and adrb2) regulate inflammation. We have previously demonstrated adrenergic modulation of chronic neuroinflammation in transgenic mouse models of AD as well as acute inflammation in primary microglia cultures using selective adrenergic pharmacology. The current studies were designed to examine *in vivo* acute immunomodulatory effects of adrenergic receptor activation on systemic and central inflammation following an acute lipopolysaccharide (LPS) challenge in mice.
C57BL/6J male mice (11-12 weeks old) were injected with selective adrenergic agonists and/or antagonists (xamoterol, salmeterol CGP 2017A, ICI 118551, metoprolol) 15 minutes prior to low threshold LPS challenge (50 ug/kg). At 90 minutes post-LPS, mice were deeply anesthetized with isoflurane, whole blood was collected from the right ventricle via cardiac puncture into lithium heparin-containing vials for plasma collection, and mice were transcardially perfused with cold phosphate buffered saline. The intact brain was removed and the right hemisphere was post-fixed (48 hours) in 4 % paraformaldehyde and the left hemisphere was frozen on dry ice. Whole blood was centrifuged and plasma was then immediately frozen on dry ice. Fresh-frozen brain and plasma were stored at -80 until later analysis of protein and gene expression for

cytokines. Fixed brain hemispheres were dehydrated in 30% sucrose, flash-frozen, and stored at -80° C for future analyses. Plasma TNFα was quantified using an ELISA kit. RNA was isolated from a 1 mm coronal brain section containing the rostral dorsal hippocampus and gene expression for TNFα, IL-1b and IL-6 were quantified by real-time polymerase chain reaction. LPS resulted in rapid induction of pro-inflammatory cytokines in plasma and gene expression in brain within 90 minutes. Xamoterol attenuated increases in both peripheral and central inflammation. These effects were prevented with an ADRB1 antagonist. We further confirmed adrenergic receptor subtype and celltype specificity in similar studies using transgenic mice with myeloid lineage conditional deletion of adrb1 or adrb2. These data support the hypothesis that adrb1 activation modulates systemic and central inflammation with implications for modulation of disease progression in Alzheimer's disease.

Disclosures: A.K. Evans: None. **B. Yi:** None. **J. Ernest:** None. **M. Shamloo:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.01/L8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Implication of lipid related risk factor for preclinical stage Alzheimer's disease: Phospholipid transfer protein (PLTP) deficiency accelerates memory dysfunction

Authors: *D. CHUI[1], Y. TONG[1], L. ZHAO[1], Y. JIN[1], D. FAN[2], X. GUO[2], H. HAN[2]
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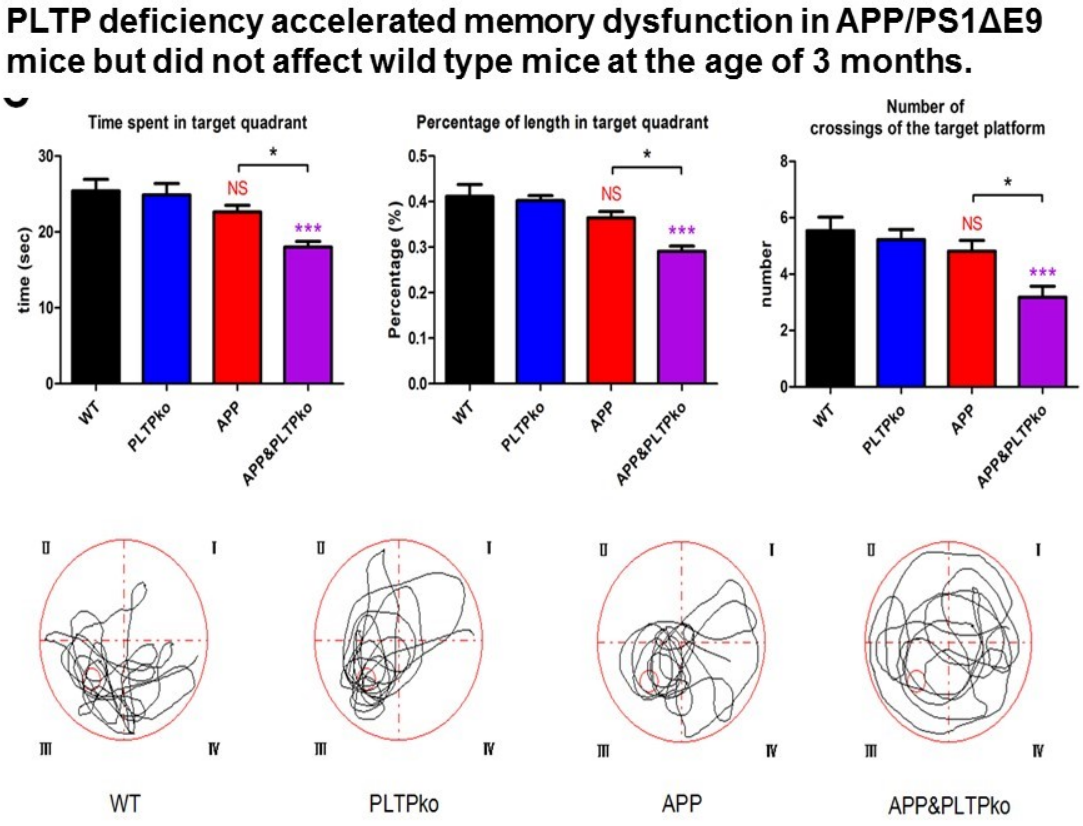
Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects the elderly. We also focus on risk factors for preclinical AD (PCAD), especially imbalance in lipid metabolism.whether deficiency of phospholipid transfer protein (PLTP) in lipid metabolism acts as a risk factor and participates in the pathological process of AD through regulating APP metabolism.[**Methodology**] APP/PS1ΔE9 mice were cross-bred to PLTPko mice to generate APP/PS1ΔE9&PLTPko mice. Morris water maze;Y-maze test;Western blot analysis;β-secretase activity assay;Quantification of Aβ peptide levels.Shotgun lipidomics analysis of brain lipids. [**Results**] PLTP deficiency accelerates memory dysfunction through altering amyloid precursor protein (APP) processing in a mouse model of AD.1) PLTP deficiency accelerated memory dysfunction in APP/PS1ΔE9 mice;2) PLTP deficiency aggravated the intracellular accumulation of Aβ;3) PLTP deficiency disrupted APP turnover ;4) PLTP deficiency enhanced the endocytic pathway for APP processing;5) PLTP deficiency up-regulated enzymes in the amyloidogenic pathway of APP;6) PLTP deficiency down-regulated BDNF;7) Impact of PLTP deficiency on brain lipid homeostasis. [Conclusion] Our current study presented a novel model with early onset

of cognitive dysfunction by PLTP deficiency in APP/PS1ΔE9 mice without appearance of amyloid deposition. Dysfunction of PLTP might be a risk factor for the elevated Aβ in the preclinical stage of AD. We first found several potential functions of PLTP deficiency in the AD model mice: impairing cognitive performance; involvement in APP trafficking/processing and intracellular Aβ generation; inducing Aβ42 related alteration of BDNF.These established PLTP deficient AD mouse models could provide insights to early stages in AD like mild cognitive impairment (MCI) or PCAD.[**Acknowledgements**]This work was supported by the No.81571044, 81571036,61625102,No. 2016YFC1305903, and 2016YFC1306302)..Thanks for the lipidomics analysis of brain lipids from Prof. Xianlin Han..



Disclosures: **D. Chui:** A. Employment/Salary (full or part-time):; 3Peking Univ. Third Hospital,, Beijing. **Y. Tong:** None. **L. Zhao:** None. **Y. Jin:** None. **D. Fan:** None. **X. Guo:** None. **H. Han:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.02/L9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG042178

AG47812

Title: Aqua-soluble ddq reduces the levels of drp1 and aβ and inhibits abnormal interactions between aβ and drp1 and protects alzheimer's disease neurons from aβ- and drp1-induced mitochondrial and synaptic toxicities

Authors: *C. KURUVA, M. MANCZAK, X. YIN, P. REDDY
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The purpose of our study was to develop a therapeutic target that can reduce Aβ and Drp1 levels, and also can inhibit abnormal interactions between Aβ and Drp1 in AD neurons. To achieve this objective, we designed various compounds and their 3-dimentional molecular structures were introduced into Aβ-Drp1 complex and identified their inhibitory properties against Aβ-Drp1 interaction. Among all, DDQ was selected for further investigation because of 1) its best docking score and 2) its binding capability at interacting sites of Drp1 and Aβ complex. We synthesized DDQ using retro-synthesis and analyzed its structure spectrally. Using biochemical, molecular biology, immunostaining and transmission electron microscopy methods, we studied DDQ's beneficial effects in AD neurons. We measured the levels of Aβ and Drp1, Aβ and Drp1 interaction, mRNA and protein levels of mitochondrial dynamics, biogenesis and synaptic genes, mitochondrial function and cell viability and mitochondrial number in DDQ-treated and untreated AD neurons. Our qRT-PCR and immunoblotting analysis revealed that reduced levels of mitochondrial fission and increased fusion, biogenesis and synaptic genes in DDQ-treated AD neurons. Our immunoblotting and immunostaining analyses revealed that Aβ and Drp1 levels were reduced in DDQ-treated AD neurons. Interaction between Aβ and Drp1 is reduced in DDQ treated AD neurons. Mitochondrial number is significantly reduced and mitochondrial function and cell viability were maintained in AD neurons treated with DDQ. These observations indicate that DDQ reduces excessive mitochondrial fragmentation, enhances fusion, biogenesis & synaptic activity and protects AD neurons against Aβ-induced mitochondrial and synaptic toxicities.

Disclosures: **C. Kuruva:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); abSynapTex LLC. **M. Manczak:** None. **X. Yin:** None. **P. Reddy:** E. Ownership Interest (stock, stock

options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); abSynapTex LLC.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.03/L10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: American Heart Association Grant-in-Aid 15GRNT25240004

Title: Beneficial effect of treadmill exercise in a rat model of sporadic alzheimer's disease

Authors: *Y. LU
Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA

Abstract: Exercise has been recently reported with its beneficial effects in the prevention and amelioration of several neurological disorders, whereas its mechanism is still elusive. The aim of our study was to investigate the potential role of treadmill exercise on streptozotocin (STZ)-induced cognitive deficit in a rat model of Alzheimer's disease (AD). Adult rats were used to induce AD type dementia by bilateral STZ intracerebroventricular injection (2.4 mg/kg), which was followed by treadmill exercise (30 min/day, 5 days/week) for 4 weeks. Our data revealed that treadmill exercise can strongly improve hippocampus-dependent cognitive functioning and robustly prevent hippocampal CA1 neuronal degeneration caused by STZ insult. Further analysis indicated a significant suppression of STZ-induced amyloid-β accumulation and tau phosphorylation. Importantly, we found that treadmill exercise can robustly attenuate reactive gliosis, and shift microglial polarization from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype, which was followed by a significant decrease in pro-inflammatory mediators and increase in anti-inflammatory cytokine expression in the hippocampus. In addition, we also found that treadmill exercise can remarkably suppress STZ-induced oxidative damage, manifested by dramatically attenuated peroxynitrite production, lipid peroxidation, and oxidized DNA damage. Finally, treadmill exercise can significantly reverse mitochondrial dysfunction caused by STZ damage, as evidenced by robust elevation in intra-mitochondrial cytochrome c oxidase activity and ATP production, as well as the consequent suppression in neuronal apoptosis. Taken together, our findings demonstrate the multifactorial effects of treadmill exercise on AD therapy, and provide more potential options in AD treatment.
Keywords: Alzheimer's disease, cognition, exercise, inflammation, microglia, oxidative stress, streptozotocin

Disclosures: Y. Lu: None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

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Program#/Poster#: 044.04/M1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R21 AG051103

VA I21 BX003023

Title: Critical changes in neurovascular coupling in hippocampal and cortical microvessels in a mouse model of Alzheimer's disease

Authors: *F. GALEFFI[1,3], D. W. KIMANI[2,3], C. A. COLTON[4], D. A. TURNER[2,3]
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Abstract: The *APPSwDI*$^{+/+}$/*mNos2*$^{-/-}$ (CVN) mouse model of Alzheimer's disease (AD) which replicates several human pathological features of AD, carries a dual mutation of APP and NOS2 (Wilcock DM et al, 2008). This model demonstrates extensive plaque formation by 36-52 weeks, and we hypothesize that abnormal neurovascular coupling and loss of cholinergic microvascular tone are key features that may be associated with plaque formation and hippocampal cell loss. We assessed changes in neurovascular coupling in the cortex and hippocampus in CVN AD mouse model as function of animal age (2-9 months old) and AD-like abnormalities in comparison to controls. We assessed changes in microvessel diameter in response to neuronal stimulation and metabolic challenges in acutely isolated mouse brain slices using live optical imaging (40X, DIC), field excitatory postsynaptic potentials (fEPSP), and DC extracellular voltage (using a submerged recording chamber at 36 °C, 95% O_2). In hippocampal slices synaptic train stimulation (10Hz, 30s) resulted in a significant increase of microvessel diameter by ~ 20 % and ~ 15 % in both wild type (n= 3) and CVN AD mice (n = 5) respectively. Similarly, brief exposure (4 min) to oxygen and glucose deprivation (OGD) resulted in a significant increase in the microvessel diameter in capillary (<10 µm diameter) and precapillary arterioles (10-13.5 µm diameter) in both hippocampal and cortical slices of CVN and wild type mice. However, in slices isolated from CVN mice the early microvascular response to OGD was attenuated, compared to wild type mice (n=6-4). In the cortex of CVN mice microvessel diameter increased by 7 ± 6 % and 2 ± 4 % and in the hippocampus by 12 ± 2 % and 3 ± 2% after OGD (4 min) and 5 minutes after reoxygenation respectively. In contrast, in wild type mice microvessel diameter increased in the cortex by 30 ± 7 % and 20 ± 3.5 % and in the hippocampus by 19.4 ± 5.5 % and 23 ± 9.5 % after OGD (4 min) and 5 minutes after reoxygenation, respectively. This difference in intrinsic microvessel metabolic reactivity to OGD

suggests that abnormal neurovascular coupling and compromised substrate delivery may be a critical step in the progression of AD.

Disclosures: F. Galeffi: None. **D.W. Kimani:** None. **C.A. Colton:** None. **D.A. Turner:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.05/M2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Neuroscience Scholar Program Professional Development Award, Society for Neuroscience (GRW)

Edmonson/Crump Professorship, Louisiana Tech University (TAM)

Title: Recently discovered alpha-7/beta-2 nicotinic acetylcholine receptor may have role in amyloid-beta pathology in Alzheimer's disease

Authors: *G. WILLIAMS, T. A. MURRAY
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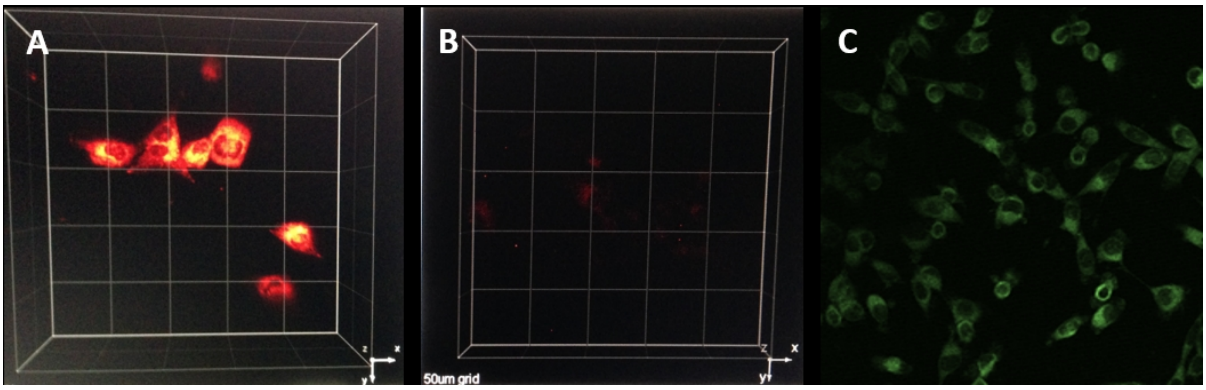
Abstract: Loss of central cholinergic neurons and accumulation of amyloid plaques are pathogenic features of Alzheimer's disease (AD). Research has shown that α7-nicotinic acetylcholine receptors (α7-nAChR) mediate amyloid-beta peptide (Aβ) internalization and contribute to neuronal death. The α7β2-nAChR, a recently-discovered nicotinic receptor subtype, is expressed in the septum and hippocampus of the brain regions of cell death early in AD. Notably α7β2 is suspected to have a higher affinity for Aβ.
Our study focused on comparing α7β2- to α7-nAChR mediated internalization of Aβ. SH-EP1 human neuroepithelial cell lines stably expressing α7-nAChRs (Fig 1A) or α7β2-nAChRs (Fig 1C), and wild type cells were incubated with oligomeric Aβ, or scrambled peptide (Fig 1B) followed by incubation with Amylo-Glo® dye (Biosensis). Fluorescence intensity was compared to determine relative amounts of Aβ internalization. Cell death assays were also performed. Cells expressing α7-nAChRs had more internalized Aβ versus cells with α7β2-nAChRs, and both were markedly higher than cells incubated with scrambled Aβ. Furthermore, cells expressing α7β2-nAChRs had a high rate of cell death. This suggests that internalization by α7β2-nAChRs could contribute to loss of function and cell death in AD. Because Aβ aggregation is a hallmark of AD pathology that contributes to neurodegeneration, further understanding the role of nicotinic acetylcholine receptors, particularly α7β2-nAChR, on amyloid-beta is crucial to working towards treatment options and preventative measures.
Figure 1.



Disclosures: **G. Williams:** None. **T.A. Murray:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.06/M3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: EU-FP7-PEOPLE program (CognitionNet; grant 607508).

Title: Hyperactivity of hippocampal Parvalbumin interneurons causes memory deficits and network imbalance in an AD mouse model

Authors: ***S. HIJAZI**[1], T. S. HEISTEK[2], H. D. MANSVELDER[2], A. B. SMIT[1], R. E. VAN KESTEREN[1]
[1]Mol. and Cell. Neurobio., [2]Integrative Neurophysiol., CNCR (VU University), Amsterdam, Netherlands

Abstract: Several studies have pointed out alterations in brain oscillatory activity as a hallmark of Alzheimer’s disease (AD). Both in AD patients and in animal models of AD, a reorganization of hippocampal and cortical network activity occurs early in AD pathogenesis. Interestingly, these network changes were reported to precede known pathologies in AD, such as amyloid plaque deposition and tau tangles, and were found to coincide with early memory decline. At the cellular level, excitation/inhibition (E/I) imbalance has been suggested to cause these network alterations. Inhibitory interneurons are believed to play an important role in this, but it remains unclear how interneuron dysfunction is causally involved in producing AD-like network alterations.
Here, using a well-established mouse model of AD, we show that hippocampal parvalbumin-positive (PV) interneurons become hyperexcitable at an early disease stage. The increased excitability of PV neurons induces changes in hippocampal pyramidal cell activity and is

causally involved in the memory deficits detected at this stage. Accordingly, inactivation of PV interneurons during learning in the Morris water maze leads to the rescue of cognitive impairments in AD mice. Furthermore, we show that prolonged activation of hippocampal PV neurons results in a persistent memory deficit in wildtype mice, and an over-excitation of the principal hippocampal network. Together, our data indicate that PV neuron functional alterations may cause some of the early clinical symptoms of AD, including hippocampal hyperexcitability, E/I imbalance and memory decline, making these neurons an attractive target for early intervention.

Disclosures: S. Hijazi: None. **T.S. Heistek:** None. **H.D. Mansvelder:** None. **A.B. Smit:** None. **R.E. Van Kesteren:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.07/M4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Deutsche Forschungsgemeinschaft

Alzheimer Forschungs Initiative

Title: Phosphorylated amyloid-β deposition in the brains of Non-Human Primates and Canines

Authors: *S. H. KUMAR[1,2], J. L. FROST[3], C. W. COTMAN[4], E. HEAD[5], R. PALMOUR[6], C. A. LEMERE[7], J. WALTER[1]
[1]Dept. of Neurol., Univ. of Bonn, Bonn, Germany; [2]Ann Romney Ctr. for Neurologic Diseases, Brigham and Women's Hospital, Harvard Med. Sch., Boston, MA; [3]Univ. of Massachusetts Med. Sch., Shrewsbury, MA; [4]UC Irvine, Irvine, CA; [5]Sanders-Brown Ctr. on Aging, Univ. of Kentucky, Lexington, KY; [6]McGill Univ. Sch. of Med., Montreal, QC, Canada; [7]Ann Romney Ctr. Neurol Dis, Brigham & Women's Hosp; Harvard Med. Sch., Boston, MA

Abstract: Progressive accumulation of amyloid β (Aβ) peptides in extracellular plaques and the cerebral vasculature is a common feature in human Alzheimer’s disease (AD), and numerous studies indicate a seminal role of Aβ in the pathogenesis of AD. Recent reports indicate a critical role of post-translationally modified Aβ variants in AD pathogenesis. Aβ can be phosphorylated at serine residue 8 (Ser8) by secreted variants of protein kinase A. Phosphorylation at this site promotes aggregation of Aβ into oligomeric and fibrillar assemblies and increases toxicity and amyloidogenecity compared to non-phosphorylated Aβ variants. Phosphorylation of Ser8 increases the stability of Aβ against proteolytic degradation by certain proteases and its clearance by microglial cells. The presence of Ser8 phosphorylated Aβ (pSer8Aβ) in human brains is

highly associated with the symptomatic state of AD indicating a critical role of phosphorylated Aβ in AD pathogenesis or as a marker for AD progression. Aβ pathology was also found in aged non-human primates and other species with an Aβ sequence identical to the human sequence. We performed immunohistochemical analysis of the Caribbean vervets and beagle canines brain tissues employing highly specific phosphorylation-state specific and general Aβ specific monoclonal antibodies. Both species revealed abundant deposition of pSer8Aβ in the form of diffuse and compact extracellular cortical amyloid plaques as well as cerebral amyloid angiopathy (CAA). An age-dependent accumulation of pSer8Aβ is observed in the Caribbean vervet brains and prefrontal cortex from aged beagle canines. Interestingly, the youngest canine showed predominantly diffuse pSer8Aβ-positive deposition. In older animals, pSer8Aβ was detected in compacted plaques as well as in CAA. Immunohistochemical analysis also revealed the presence of pSer8Aβ in the dense-core compacted plaques or neuritic plaques and in and around microvessels in vervet brains. The data indicate that age-dependent accumulation of phosphorylated Aβ in the brain is a common feature of humans, non-human primates and other species with homologous amino acid sequence of Aβ. Thus, Aβ might undergo similar post-translational modification by phosphorylation in these species, further supporting similar pathophysiological mechanisms resulting in aggregation and deposition of Aβ. Further research employing these natural animal models would be interesting and relevant for investigating the role of phosphorylation in AD pathogenesis, to test novel diagnostics, and to develop effective therapeutic strategies for AD.

Disclosures: S.H. Kumar: None. **J.L. Frost:** None. **C.W. Cotman:** None. **E. Head:** None. **R. Palmour:** None. **C.A. Lemere:** None. **J. Walter:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.08/M5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Project no. LQ1605 from the National Program of Sustainability II (MEYS CR)

project FNUSA-ICRC no. CZ.1.05/1.1.00/02.0123 (OP VaVpI)

Title: Role of APP axonal transport in Alzheimer’s disease and chronic traumatic encephalopaty

Authors: *V. LACOVICH, V. M. POZO DEVOTO, M. CARNA, K. TEXLOVA, M. FEOLE, G. STOKIN
Intl. Clin. Res. Ctr. FNUSA-ICRC, Brno, Czech Republic

Abstract: Although amyloid precursor protein (APP) and microtubule-associated protein tau have been shown to play a major role in the pathogenesis of Alzheimer's Disease (AD) and more recently in the Chronic Traumatic Encephalopathy (CTE), the mechanisms underlying their role in the pathogenesis of these neurodegenerative disorders remain unclear. Accumulating evidence suggests that perturbed axonal transport plays an early and possibly causative role in the pathogenesis of AD and CTE. This project tests further the role of perturbed axonal transport in neurodegeneration with particular emphasis on dynamic changes in APP and tau, since knowledge about these changes will also contribute to a better understanding of frequently equally dynamic behavioral and cognitive changes in AD and CTE. We have developed a novel cell culture paradigm to assess in vivo dynamic changes in axonal APP and tau following injury. This paradigm consists in specifically designed microfluidic chamber coupled to an electronically controlled syringe pump, which induces sheared stress in the axons. Moreover, microfluidic chamber is populated by human stem cell derived mature neurons. This set up altogether allows for real time APP imaging in response to axonal injury. Results obtained with this cell culture paradigm are coupled to a well-established mouse traumatic brain injury model to allow for confirmation of cell culture findings in an in vivo setting. Neurons differentiated from H9 derived human neural stem cells were characterized by RT-PCR, FACS, immunochemistry and electrophysiology. We found that sheared stress induced axonal injury results in selective and immediate perturbation of the axonal transport of APP and these finding were further confirmed in a mouse model of traumatic brain injury. Considering our recent results identified subtle perturbations in tau isoforms as sufficient to trigger perturbations in the axonal transport of APP we next addressed whether axonal perturbations of APP also result in changes in tau. Our finding disclose an intimate bidirectional link between APP and tau in AD and CTE, which sheds new light to the mechanisms involved in the development of neurodegeneration.

Disclosures: V. Lacovich: None. **V.M. Pozo Devoto:** None. **M. Carna:** None. **K. Texlova:** None. **M. Feole:** None. **G. Stokin:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant 1R15AG050292

Alzheimer's Association Grant NPSPAD 247219

Title: Central inhibition of amylin receptors blocks beneficial effects of peripherally administered amylin in Alzheimer's disease

Authors: *R. R. CORRIGAN[1], J. GRIZZANTI[1], M. PALLAS[3], A. CAMINS[3], G. CASADESUS[2]
[1]Biomed. Sci., [2]Biol. Sci., Kent State Univ., Kent, OH; [3]Dept. of Pharmacol. and Therapeut. Chem., Univ. de Barcelona, Barcelona, Spain

Abstract: Peripheral administration of the recombinant form of the metabolic peptide amylin (pramlintide) rescues spatial memory and reduces amyloid-beta plaques in AD mouse models. To elucidate whether amylin's therapeutic effects are mediated through amylin receptors within the brain or peripherally by improving metabolic function, APP/PS1 mice were chronically treated with pramlintide while simultaneously treated intracerebroventricularly with the amylin receptor antagonist AC187. Preliminary results indicate that CNS blockade of amylin receptors abolishes the therapeutic effects seen by peripheral administration of amylin, specifically, improvements in cognition and reductions in amyloid-beta plaque burden. Together these data suggest that the neuroprotective effects of peripheral amylin therapy are mediated through action in the CNS rather than simply improving peripheral metabolic function.

Disclosures: R.R. Corrigan: None. **J. Grizzanti:** None. **M. Pallas:** None. **A. Camins:** None. **G. Casadesus:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.10/M7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DA09082 to E. J. V.

MH100319 to S. A. T.

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Title: Consequences of noradrenergic depletion on endogenous amyloid beta$_{42}$ levels in the medial prefrontal cortex

Authors: *J. A. ROSS[1], B. A. S. REYES[1], S. A. THOMAS[2], E. J. VAN BOCKSTAELE[1]
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Abstract: The locus coeruleus (LC)-norepinephrine (NE) system is an understudied circuit in the context of Alzheimer's disease, and is thought to play an important role in neurodegenerative and neuropsychiatric diseases involving catecholamine neurotransmitters. As a cluster of

noradrenergic neurons located at the base of the fourth ventricle with broad-reaching efferents providing NE to the entire neuraxis, the LC is recognized as the sole provider of NE to the frontal cortex and hippocampus. While it is known that NE may influence levels of amyloidβ_{42} ($A\beta_{42}$) via interactions with adrenergic receptors (AR) on neurons or microglia to promote production or degradation of $A\beta_{42}$, the functional relevance of NE in modulating endogenous $A\beta_{42}$ levels has not been studied. This study utilized two models of NE depletion, N-(2-chloroethly)-N-ethyl-2-bromobenzyllamine hydrochloride (DSP-4) lesion and dopamine β hydroxylase (DβH) knockout (KO) mice, and revealed reduced levels of endogenous $A\beta_{42}$, without changes in amyloid precursor protein (APP) cleavage products. DSP-4 treated male and female rats (0.54 pg/mg; SD 0.4) showed significantly decreased levels of $A\beta_{42}$ as quantified by ELISA (ANOVA p=0.005; F=7.15; df=18), compared to naïve (1.15 pg/mg; SD 0.43;Tukey's adj. p=0.01) and saline-treated (1.186 pg/mg; SD 0.18; Tukey's adj. p=0.009) controls. Western blot analysis of APP-α , APP-β, and BACE 1 expression showed no significant changes between naïve, DSP-4- and saline-treated rats. We then evaluated a genetic model of NE depletion for alterations in endogenous $A\beta_{42}$. A significant decrease in $A\beta_{42}$ levels was observed in male (p=0.002) and female (p=0.03) DβH KO mice compared to heterozygous controls. Western blots were used to determine if decreased $A\beta_{42}$ levels result from altered β-secretase (BACE1) expression; however, no significant changes were observed, consistent with unaltered sAPP-β and β C-terminal fragments. Correspondingly, there were no significant changes in APP-α or ADAM10 expression in precursor, mature, or active forms. The significant decrease in $A\beta_{42}$ monomers is likely the result of decreased interactions of NE with the β_2 AR or α_{2a}AR, which are known to promote $A\beta_{42}$ production and secretion upon stimulation by NE. Alternatively, the observed decreases in $A\beta_{42}$ may be the result of decreased neuronal activity of NE-synthesizing neurons.

Disclosures: **J.A. Ross:** None. **B.A.S. Reyes:** None. **S.A. Thomas:** None. **E.J. Van Bockstaele:** None.

Poster

044. APP: Animal and Cellular Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Hassel Family Foundation

F30AG048710

NS085171

Title: Programs of neuronal function regulated by ΔFosB are shifted and expanded in an Alzheimer's disease mouse model

Authors: *G. S. STEPHENS[1], J. C. YOU[2], K. ANISHCHENKO[1], C.-H. FU[1], X. ZHANG[1], Y. LIU[3], J. CHIN[1,2]
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Abstract: Alzheimer's disease (AD) is accompanied by cognitive decline, the severity and rate of which correlate with seizure activity. Experiments in AD patients and mouse models now suggest a causal role for seizures and epileptiform activity in cognitive decline. Therefore, understanding the mechanisms by which seizures induce cognitive decline may enable the discovery of novel therapeutic targets. We found that in the hippocampus of human amyloid precursor protein (hAPP) transgenic mice, seizure activity dramatically upregulates expression of the transcription factor ΔFosB. The unusually long half-life of ΔFosB (~8 days) allows even infrequent seizures to produce long-lasting ΔFosB accumulation that may contribute to persistent cognitive deficits. We found that inhibition of ΔFosB signaling ameliorates cognitive deficits in hAPP mice, suggesting that ΔFosB plays a critical role in cognition. ΔFosB may epigenetically regulate cognition by interacting with various histone modification enzymes to alter gene expression. We have combined unbiased ChIP- and RNA-sequencing analyses with gene ontology (GO) clustering to identify candidate genes and putative neuronal functions regulated by ΔFosB in the hippocampus of hAPP and non-transgenic (NTG) mice. Quantitative reverse transcription PCR and immunohistochemical experiments in independent cohorts of mice confirmed that hippocampal expression levels of ΔFosB target genes were indeed altered. Only 4% of total genes bound by ΔFosB were shared between the genotypes, and included genes involved in cell-cell adhesion and regulation of cell differentiation. In NTG mice, ΔFosB largely bound genes that regulate neurodevelopmental programs such as synapse maturation and Wnt signaling. However, in hAPP mice, the repertoire of ΔFosB-bound genes was shifted to include genes that regulate excitability and synaptic transmission, suggesting potential mechanisms that could impact memory and neuroprotection. Overall, our data suggest that seizure-induced ΔFosB accumulation in hAPP mice may regulate multiple aspects of hippocampal neuronal function to alter cognition in AD.
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Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant MH107456

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Title: Quantitative study of white matter neurons in the corpus callosum, cingulum bundle, and anterior commissure in wildtype and APP.PS1 mice

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Abstract: Mice, like primates and other mammals, have a population of neurons in the subcortical white matter (WM). How these white matter neurons (WMNs) change in different experimental conditions and in mouse models of disease is unknown. In humans, increased density of WMNs is reported in schizophrenia (Connor et al., 2011), and dendritic changes are reported in association with amyloid plaques (e.g., Kowall & Beal, 1988). For evaluating changes in density and subtype of WMNs, baseline quantitative data are necessary. In this study, we used immunohistochemistry (IHC) for the pan-neuronal marker NeuN and scored total population of WMNs in several white matter regions (ROIs): namely, the corpus callosum and its laterally adjoining white matter (CC), the cingulum bundle (CG), and the anterior commissure (AC). Coronal sections (50 µm thickness, with 300 µm inter-section intervals) were digitized (10X objective) and frames stitched using the “Grid/Collection stitching” FIJI plugin (Preibisch et al., 2009). ROIs were outlined, cells were manually counted, and data were recorded by ImageJ. In 12-month-old wildtype mice (WT, n = 9), the CC (bilateral; from Bregma 1.1 to -2.1) contained a mean of 81 neurons/section, ranging from a low of 73 to a high of 92, and the estimated total number of WMNs was 5,200 (calculated from 10 sections spaced across 3.2 mm). For the overlying CG (unilateral), WT mice had a mean of 51 neurons/section. For the AC (unilateral; from Bregma 1.5 to 0.5), WT mice had a mean of 4 neurons/section. In a parallel series from the same brains, double IHC for NeuN and GAD65/67 showed that, consistent with previous studies in other species, WMNs comprise both excitatory and inhibitory neurons, with GABAergic inhibitory (GAD65/67+) neurons being on average 34% of total WMNs in our CC ROI. The same procedures and analyses were applied to the APP.PS1 mouse model of Alzheimer’s disease (MGI ID: 3524957). The brains of 12-month-old APP.PS1 mice (n = 15) had a mean of 76 neurons/section (range: 56 to 89) in the CC with an estimated total of 4,800 WMNs. APP.PS1 mice had a mean of 51 neurons/section in the CG and 4 neurons/section in the

AC, as sampled to date. In APP.PS1 mice, GAD65/67+ WMNs were 30% of the total (determined for CC). Further IHC screens identified nitrergic (nNOS+) and calretinin+ subpopulations, as well as some double-labeled neurons, in both WT and APP.PS1 mice. Preliminary data suggest that there is a 31% loss of the nitrergic population in the CC of APP.PS1 mice and also nNOS+ dendritic dystrophy. This is consistent with reports in Alzheimer's patients that dendritic dystrophy of nitrergic neurons is associated with amyloid plaques in white as well as gray matter regions.

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Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant-AG042178

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Garrison Family Foundation

Title: Reduced dynamin-related protein 1 mitigates mitochondrial fragmentation, elevates spatial learning and memory functions and elevates dendritic spines in app transgenic mice

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Abstract: The purpose of our study is to understand the protective effects of reduced levels of mitochondrial fission protein Drp1 against amyloid beta (Aβ) induced mitochondrial abnormalities and synaptic deficiencies in Alzheimer's disease (AD) pathogenesis. Mounting evidence suggests that Aβ-induced mitochondrial dysfunction and synaptic damage are largely involved in AD progression and pathogenesis. We recently found that abnormal physical interaction between Drp1 and Aβ, leading to excessive mitochondrial fragmentation, reduced mitochondrial fusion
In the current study we continued to explore the reduced Drp1 biological functions in lieu of spatial learning and memory, synaptic numbers and mitochondrial number/size along with the expression of mitochondrial division/fusion proteins, synaptic proteins, and biogenesis proteins in 12-month-old APPXDrp1+/- relative to the 12-month-old APP mice. Our findings suggest that a partial reduction of Drp1 increased synaptic buttons (Golgi-cox) may potentially be effective in

ameliorating cognitive function (Morris-water maze). In addition, reduced Aβ production in APPXDrp1+/- mice eventually reduced mitochondrial dysfunction, and maintains mitochondrial dynamics, enhances mitochondrial biogenesis and synaptic plasticity. Partial reduction of Drp1 may serve as therapeutic regime in preventing Alzheimer's disease.

Disclosures: **M. Manczak:** A. Employment/Salary (full or part-time):; full, Garrison Institute on Aging Texas Tech Univesity. **R. Kandimalla:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **M. Vijayan:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **X. Yin:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **C. Kuruva:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **S. Kumar:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **P. Reddy:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center.

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044. APP: Animal and Cellular Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Research Funding for Longevity Sciences (25-20) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

Title: Dynein dysfunction impedes retromer trafficking and concomitant disruption of retrograde trafficking is required for the alteration in APP metabolism

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Abstract: It is widely accepted that beta-amyloid protein (Abeta) plays a pivotal role in Alzheimer's disease (AD) pathogenesis, and accumulating evidence suggests that endocytic dysfunction is involved in Abeta pathology. The retromer complex is a key element of the endosomal protein sorting machinery, and it mediates the retrograde trafficking of cargos from endosomes to the trans-Golgi network (TGN). Importantly, recent genome-wide association studies identified retromer-related genes such as SORL1 and VPS35 as a risk factor for AD, and

several studies showed that retromer deficiency enhances Abeta pathology both in vitro and in vivo. Cytoplasmic dynein, a microtubule-based motor protein, mediates minus end-directed vesicle transport via interactions with dynactin, another microtubule-associated protein that can also interact with retromer. We previously showed that aging attenuates the dynein-dynactin interaction and that dynein dysfunction reproduces age-dependent endocytic disturbance, leading to the intracellular accumulation of beta-amyloid precursor protein (APP) and its beta-cleavage products including Abeta. Here, we report that aging itself affects retromer trafficking in nonhuman primate brains, and that dynein dysfunction reproduces age-dependent retromer deficiency such as the endosomal accumulation of retromer-related proteins as well as its cargos. Moreover, we demonstrated that the siRNA-mediated disruption of each retrograde endosome trafficking pathway did not alter endogenous APP metabolism such as observed in aged monkey brains and dynein-depleted cells. These findings suggest that dynein dysfunction can cause retromer deficiency and that concomitant disruption of retrograde trafficking pathways may be the key factor underlying age-dependent Abeta pathology.

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Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: EU Horizon 2020, Human Brain Project, Grant 720270

EU JPND project CrossSeeds, NFR Grant 247995

Title: Workflow for automated quantification and spatial analysis of Alzheimer’s plaque labeling in microscopic rodent brain sections

Authors: *S. C. YATES[1], M. PUCHADES[1], C. COELLO[1], A. KRESHUK[2], T. B. LEERGAARD[1], J. G. BJAALIE[1]
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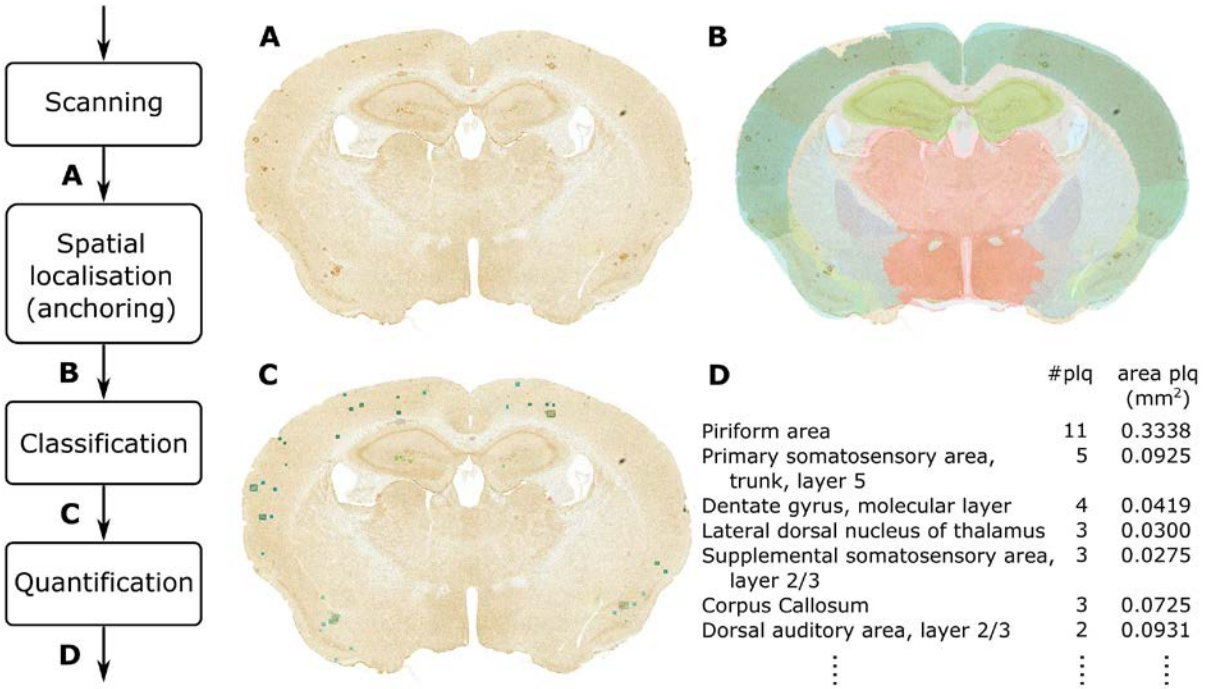
Abstract: Introduction: Automated analysis of series of microscopic images from rodent brains can to advantage be used in many neuroscience research projects. To this end, we present a workflow for the automated quantification and spatial analysis of labeling in large series of section images from rodent brain. As an example, we present the quantification of Alzheimer’s disease plaques across a whole mouse brain series immunohistochemically stained for the APP

N-terminus (1D1).

Method: As a first step, the whole brain image series was anchored to the Allen mouse brain atlas, using an in-house software tool (QuickNII), to produce accurate anatomical maps adapted to the orientation of the images. Subsequently, the section images were classified by use of the *ilastik* software tool, based on supervised random forest learning algorithms. The classifier relies on input from manual user annotations of selected training images and the image features intensity, edge and texture. In a separate process, the class corresponding to plaque staining was cleaned, to remove edge artifact and background noise. The classified images were subsequently analyzed on a whole brain and regional level with input from the atlas maps. Thereby, a list of individual plaque features (area, location, etc.), region level features (number of plaques, area of plaques, etc.) and whole brain features were derived, enabling quantitative regional analysis as a semi-automatic pipeline.

Results: With limited user interaction, we identified and localized according to brain region, individual amyloid plaques across a whole brain image series (Figure 1). Further validation of the workflow is on-going.



D	#plq	area plq (mm^2)
Piriform area	11	0.3338
Primary somatosensory area, trunk, layer 5	5	0.0925
Dentate gyrus, molecular layer	4	0.0419
Lateral dorsal nucleus of thalamus	3	0.0300
Supplemental somatosensory area, layer 2/3	3	0.0275
Corpus Callosum	3	0.0725
Dorsal auditory area, layer 2/3	2	0.0931
⋮	⋮	⋮

Disclosures: **S.C. Yates:** None. **M. Puchades:** None. **C. Coello:** None. **A. Kreshuk:** None. **T.B. Leergaard:** None. **J.G. Bjaalie:** None.

Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grant of National Research Foundation of Korea; NRF-2015R1A2A1A15052049

Title: Changes in the pathogenesis of alzheimer's disease in clusterin-deficient 5xFAD transgenic mice

Authors: *J.-Y. LEE[1], S.-B. OH[2], T. KIM[2], M. KIM[2], D. KIM[2]
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Abstract: Clusterin (CLU), also called Apolipoprotein J (ApoJ), has been suggested as an important risk factor for late-onset Alzheimer's disease by recent large genome-wide association studies (GWAS). Clusterin is known to interact with amyloid-β (Aβ) molecules as a chaperone protein and participate in the pathogenesis of Alzheimer's disease, but conflicting evidences are currently presented as to whether it promotes or inhibits amyloid pathogenesis. An early animal study found that clusterin may aggravate amyloid pathogenesis and toxicity in the human amyloid precursor protein (APP)-transgenic mouse model of Alzheimer's disease, whereas most in vitro and biochemical studies are still focused on its beneficial effects or mechanisms that reduce the pathogenesis.
To determine the role of endogenous clusterin in the pathogenesis of Alzheimer's disease, we generated the clusterin-deficient 5xFAD hAPP transgenic mice and evaluated the changes in amyloid pathogenesis, cognitive impairment, and the expression levels of synaptic or neuronal activity-associated proteins in the mice. At 5 months of age, they showed the significantly lower levels of Aβ contents (including soluble-, insoluble, monomeric, oligomeric, aggregated or total Aβ molecules) and Aβ depositions (including Aβ-immunoreactive or Congophilic plaques) in the brain compared to their littermate clusterin-expressing 5xFAD mice. Clusterin deficiency also led to the improvement of learning and memory performance along with the modifications in expression of synaptic or neuronal activity-related signal molecules. On the other hand, those improvement effects of clusterin deletion on the pathogenesis of Alzheimer's disease almost disappeared by 9-10 months of age, when Aβ deposition exceeded the maximum in the brains of 5xFAD mice.
These results indicate that clusterin is an important endogenous factor facilitating the pathogenesis of Alzheimer's disease in the earlier stage of amyloid pathogenesis, but its influence is weakened or lost in the late stage when amyloid pathogenesis has already severely

worsened. Therefore, we think that clusterin would involve in the pathogenesis of Alzheimer's disease via triggering or facilitating the amyloid pathogenesis.

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Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5R01AG048993

Title: Defining the temporal progression of Alzheimer's disease in the brain vs. intestine

Authors: *G. D. MANOCHA[1], A. M. FLODEN[1], N. M. MILLER[1], A. SMITH[2], K. NAGAMOTO-COMBS[3], T. SAITO[4], T. C. SAIDO[5], C. K. COMBS[1]
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Abstract: Due to its dementing characteristic, Alzheimer's disease (AD) is often characterized by fibrillar amyloid-beta (Aβ) peptide containing plaques and associated reactive microglia in the brain. However, the elderly are also often afflicted with intestinal dysfunction such as constipation or fecal incontinence which could be due to degenerating, proinflammatory changes in the enteric nervous system. Based upon the fact that enteric neurons also express APP we hypothesized that the enteric nervous system may demonstrate Aβ production and deposition along with associated inflammatory changes and behavioral dysfunction during progression of AD that may be temporally unique from changes in the brain. To test this idea, we compared C57BL/6 wild type male and female mice to two models of AD, littermate control APP/PS1 mice and the newly characterized APP (NL-G-F) mice at 3, 6, and 12 months of age. Brain amyloid plaque deposition, microgliosis, astrogliosis, and oligomeric and fibrillar Aβ deposition in APP (NL-G-F) and APP/PS1 mice were increased in an age-dependent manner. The increase in gliosis, oligomeric, and fibrillar Aβ in both male and female APP (NL-G-F) mice preceded that observed in the APP/PS1 mice, observable by 3 months of age. APP (NL-G-F) also demonstrated reduced Aβ 1-40 levels compared to the APP/PS1 mice at 3 months of age correlating with the Iberian mutation to promote a higher Aβ 1-42/1-40 ratio. Interestingly, female but not male APP/PS1 and APP (NL-G-F) mice demonstrated memory dysfunction at 3 months of age. In addition, 3 month old female APP (NL-G-F) mice also presented decreased intestinal motility as compared to the wild type and APP/PS1 mice. However, 3 month old female APP/PS1 mice demonstrated significantly increased intestinal permeability compared to wild type and APP (NL-G-F) mice. These data demonstrate that both AD mouse models have

cognitive and intestinal dysfunction by 3 months of age correlating with Aβ production. Interestingly, the unique nature of Aβ production and deposition as well as intestinal changes across the two mouse models suggests that further study is required to better characterize the brain and peripheral disease progression for ultimate comparison to human disease.

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044. APP: Animal and Cellular Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Multiple mechanisms of dimethylfumarate in amyloidβ -induced neurotoxicity in an *In vitro* and *In vivo* models of Alzheimer's disease

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Abstract: Much of the research on Alzheimer disease has focused on the importance of oxidative processes in disease pathogenesis. Cellular changes demonstrated that oxidative and inflammatory stresses are events that precede the manifestation of the hallmark pathologies of the disease such as neurofibrillary tangles and senile plaques. Dimethyl fumarate (DMF) is an orally bioavailable methyl ester of fumaric acid and activator of Nrf2 with potential neuroprotective and immunomodulating activities. Therefore, the aim of the present work was to evaluate the potential beneficial effects of DMF in an in vitro Alzheimer's model on SH-SY5Y neuroblastoma cell lines stimulated with amyloid-beta (Aβ) and in an in vivo model on transgenic Tg (APPswe,PSEN1dE9) mice. In in vitro studies was observed that DMF pretreatment (30 μM) preserved cellular viability from Aβ 1μM stimulation, reducing tau phosphorylation. Moreover, DMF was able to induce an activation of manganese superoxide dismutase (Mn-SOD) and hemeoxygenase- 1 (HO-1), decreasing the severity of oxidative stress. Furthermore, studies in vivo demonstrated that DMF treatment (30 mg/kg, oral gavage) for 30 days significantly reduced Aβ plaque in the brain cortices and hippocampus, improved spatial memory retention, reducing microgliosis and oxidative stress. Our results showed important protective effects of DMF pretreatment from Aβ stimulation in SH-SY5Y cells and in Tg APP/PS1 mice, highlighting a Nrf2/ NF-κB dependent mechanism, that could provide a valuable support to the therapies for neurodegenerative diseases today.

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Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Disorganized steady state visually evoked potentials in amyloid beta overproducing mice

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Abstract: Recently, there has been an increasing interest to identify neurophysiological abnormalities in Alzheimer's disease (AD) patients as well as in transgenic animals capturing certain aspects of AD pathology. In addition to spontaneous neuronal activity, sensory evoked potentials have also been investigated. Particularly, disturbances in visual processing have been reported as a common feature in AD patients (Jacob et.al. 2001) and has been demonstrated electrophysiologically. It is along these observations that in the present study we investigated cortical processing of visual stimuli in amyloid beta (Aβ) overproducing TG2576 mice whereby steady state visually evoked potentials (SSVEP's) were acquired from primary visual cortex in response to sustained 40Hz light pulse trains in, RD1 screened, transgenic (n=8) and WT controls (n=10) at 7 months of age. The resulting epochs were subjected to frequency domain analyses where evoked, induced and spontaneous gamma power, in addition to inter-trial phase coherence (ITPC) were measured to identify genotype specific anomalies. All SSVEP's were normalized to the pre-stimulus background gamma (30-50Hz) as this band was observed to be significantly enhanced in the transgenic group (p=0.001, two-tailed, unpaired t-test; 49±0.38 versus 46.6±0.45 dB). Analyses of SSVEP's revealed that evoked, or phase-locked, peak gamma power is significantly reduced (p =0.004; -25.8±7%; two-tailed unpaired t-test) in TG2576 with induced peak gamma in the same band being less affected (p=0.0375, two-tailed, unpaired t-test; -0.7±0.3%). Furthermore, steady-state ITPC is significantly reduced (p=0.002, two tailed unpaired t-test) in TG2576 when compared to age matched WT controls (0.26±0.02 versus 0.39±0.03 respectively). Based on these findings, it is concluded that Tg2576 mice have a significantly diminished "signal to noise" ratio, as it relates the temporal processing of sustained visual stimuli in primary visual cortex. Further studies are warranted to determine if SSVEP's could have diagnostic potential for identifying individuals with Alzheimer's disease related pathologies.

Disclosures: **B.D. Harvey:** None. **E. Morozova:** None. **M. Hajos:** None.

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NIH Grant NS034467 to B.V.Z.

NIH Grant HL052246 to J.H.G.

Title: Murine 3K3A-activated protein C has anti-amyloidogenic effect in the 5xFAD mouse model of Alzheimer's disease

Authors: *A. P. SAGARE[1], D. LAZIC[1], E. LAWSON[1], A. GO[1], J. A. FERNANDEZ[2], J. H. GRIFFIN[2], B. V. ZLOKOVIC[1]
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Abstract: Activated protein C (APC) is an endogenous plasma serine protease with multiple actions including anticoagulant, cytoprotective, vasculoprotective and anti-inflammatory activities. Previous studies by our group have shown that APC is neuroprotective and promotes neurogenesis in vivo and recovery after ischemic stroke and traumatic brain injury in rodents. Here, we tested the effect of an analog of murine APC with ablated anticoagulant activity but preserved cell signaling activities, such as 3K3A-APC on reduction in amyloid pathology in 5xFAD mice, an animal model of Alzheimer's disease (AD). Three-month-old 5xFAD transgenic mice that overexpress mutant human APP with three familial AD (FAD) mutations along with human presenilin 1 harboring two FAD mutations in the brain were treated intraperitoneally with 100 µg/kg/day 3K3A-APC or vehicle for four months. Compared to vehicle treatment, 5xFAD mice treated with 3K3A-APC showed a significant reduction in Aβ40 and Aβ42 in the hippocampus and cortex by 40-50% and 50% reduction in Thioflavin-S-positive amyloid plaques. 3K3A-APC treatment prevented nuclear translocation of nuclear factor kappa B (NF-κB) and suppressed NF-kB and NF-κB-regulated gene expression which resulted in a reduction of β-secretase activity and neuroinflammation in the brain. Furthermore, mice treated with 3K3A-APC showed a significant reduction in blood-brain barrier breakdown and accumulation of blood-derived neurotoxic proteins in the brain. 3K3A-APC-treated 5xFAD mice showed improved cerebral blood flow responses and hippocampal-dependent cognitive functions. Thus 3K3A-APC holds potential as a promising anti-amyloidogenic therapy for patients with mild or moderate AD.

Disclosures: **A.P. Sagare:** None. **D. Lazic:** None. **E. Lawson:** None. **A. Go:** None. **J.A. Fernandez:** None. **J.H. Griffin:** None. **B.V. Zlokovic:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.21/N8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AIIMS Intramural Project

Title: Targeting 5-LOX in Alzheimer's disease: Potential serum marker and in-vitro evidences for rescue of neurotoxicity by its peptide inhibitor

Authors: *S. SHEKHAR, N. RAI, Y. YADAV, A. B. DEY, S. DEY
AIIMS, New Delhi, India

Abstract: In recent years is noticed that inflammatory process plays a key role in neurodegenerative disorder. Pro-inflammatory molecule, 5-Lipooxygenase (5-LOX), protein is involved in pathologic phenotype of AD.It includes Aβ amyloid deposition and tau hyper phosphorylation both. This study determined the level of 5-LOX in serum of Alzheimer's disease (AD) patient, Mild cognitive impairment (MCI), normal elderly and rescue effect by YWCS, a peptide inhibitor of 5-LOX on neurotoxicity by Aβ amyloid$_{25-35}$ (Aβ_{25-35})in neuroblastoma cells SH-SY5Y. The level of serum 5-LOX was estimated by surface plasmon resonance and presence of 5-LOX in serum was confirmed by western blot. The neuroprotective effect of 5-LOX peptide inhibitor YWCS in Aβ_{25-35} induced neurotoxicity was analyzed by MTT assay and western blotting. We found significant high level of serum 5-LOX in AD patients and also in MCI compare to normal control group. The peptide inhibitor of 5-LOX, YWCS prevented neurotoxic effect of A$\beta_{25-35}$by reducing the expression of γ -secretase as well as p-Tau$_{181}$in SH-SY5Y cells. However, YWCS was nontoxic towards normal HEK cells. The differential expression of serum 5-LOX among the study groups suggests, it can be one of potential serum protein marker and therapeutic regimen for AD and MCI. The downhill correlation with neuropsychological parameters i.e. MoCA and HMSE increases its importance and make it useful during clinical setup which is very needful in developing countries. Peptide YWCS, can serve as new platform as 5-LOX inhibitor which can prevent neurotoxicity developed in AD.

Disclosures: **S. Shekhar:** None. **N. Rai:** None. **Y. Yadav:** None. **A.B. Dey:** None. **S. Dey:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.22/N9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association Grant 2016-MNIRGD-391961

Title: Social deficits in the 5xFAD mouse model of Alzheimer's disease

Authors: *F. KOSEL, P. TORRES MUNOZ, T. B. FRANKLIN
Psychology and Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: Behavioural assays examining animal models of Alzheimer’s disease (AD) tend to focus on memory and cognitive function. However, AD patients also present with a number of neuropsychiatric symptoms including increased agitation and aggression, increased anxiety and depressive symptoms, increased irritability, and social impropriety. We are currently investigating whether the 5xFAD transgenic mouse model of AD can be used to model the social deficits observed in AD patients. Specifically, this study investigates responses to social cues, social preference, social recognition, and aggression in transgenic and wild-type female and male mice across lifespan. Preliminary results suggest that male 5xFAD mice exhibit increased scent marking in the presence of urine from opposite-sex conspecifics, as well as increased aggression, compared to wild-type mice, while female 5xFAD mice exhibit increased preference for novel over familiar social interaction. This research suggests that the 5xFAD strain may be a useful model for studying the neural bases for social deficits related to AD.

Disclosures: F. Kosel: None. **P. Torres Munoz:** None. **T.B. Franklin:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.23/N10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Region Skåne

JPND

Title: *In vitro* prion-like seeding of intracellular beta-amyloid in an APP expressing cell line

Authors: T. T. OLSSON, O. KLEMENTIEVA, *G. K. GOURAS
Lund Univ., Lund, Sweden

Abstract: Alzheimer's disease (AD) brain tissue can act as a seed to accelerate aggregation of beta-amyloid (Aβ) into plaques in AD transgenic mice. Aβ seeds have been hypothesized to accelerate plaque formation in a prion-like manner of templated seeding and spreading via anatomical pathways. However, the nature of the propagating Aβ seed in brain remains unclear. Not all forms of Aβ, including untreated synthetic Aβ1-42 or Aβ from CSF of AD patients, are capable of prion-like seeding *in vivo*. In contrast to tau and α-synuclein, the cellular mechanisms of Aβ propagation have not been explored. Although amyloid plaques are extracellular, numerous studies support an early and important role of intraneuronal Aβ in the pathogenesis of AD. We hypothesize that intracellular Aβ can be a propagating, prion-like strain. Here we induce prion-like Aβ in a cell-line analogous to what has been shown for the prion-like proteins tau and α-synuclein.
We treat N2a cells expressing APP with the Swedish mutation with aged mutant APP/PSEN1 transgenic mouse brain homogenate or aged WT brain as a control. Only the AD transgenic brain extracts induce aggregation of Aβ in a subset of cells, and by performing single cell cloning, we isolated these cells containing Aβ aggregates. We use blue native PAGE, immunohistochemistry and Fourier transform infrared spectroscopy to determine Aβ aggregation. We see that the intracellular Aβ aggregates are stable over multiple cell divisions and passages, providing evidence that cellular Aβ aggregates can be induced and sustained *in vitro*. To determine whether intracellular Aβ by itself can act as a seed to induce aggregation of Aβ, we treated naive cells with cell lysates of the prion-like N2a cells containing Aβ aggregates. Only treatment with cell lysates from cell clones containing seeded Aβ aggregates, but not from control cell lines, induced aggregation of Aβ in the previously naive cells.
Our data strengthen the case that Aβ acts as a prion-like protein, demonstrate that propagating Aβ seeds can be produced intracellularly and provide an *in vitro* model of nucleated seeding of Aβ.

Disclosures: T.T. Olsson: None. **O. Klementieva:** None. **G.K. Gouras:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.24/N11

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The impact of phospholipase D functional ablation in an Alzheimer's disease *Caenorhabditis elegans* model

Authors: *A. F. BRAVO[1], J. D. SILVA[1], R. B. CHAN[2], G. D. PAOLO[2], A. T. CASTRO[1], T. G. OLIVEIRA[1]
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Abstract: Lipids are a major constituent of the brain and specifically signaling lipids have been shown to regulate brain functioning.Moreover, lipid signaling modulation has been demonstrated to be a potential therapeutical option for neurological disorders, such as Alzheimer´s Disease (AD).Growing evidence suggests that a group of enzymes called phospholipases, that modulate signaling lipids, have an impact in neuronal physiology. In this study, we focused on a specific enzyme, phospholipase D (PLD). In order to study the role of this enzyme, in physiology and in disease context, we used a nematode model with PLD functional ablation (PLDmut) and overexpression of amyloid beta (Aβ), as an AD-like model.A multitude of behavioral tests, confocal imaging and biochemical analysis were performed using PLDmut; Aβ overexpressing; bigenic PLDmut/Aβ C.elegans and as a control group wild type strain (N2). A decrease in PLD activity was confirmed in PLDmut animals by mass spectrometry analysis, as well as mechanistically through evaluation of ethanol susceptibility, since PLD has an increased affinity to primary alcohols.Our data indicates that although PLD is a key signaling modulator, it is not essential for the survival or for the normal performance in a myriad of behavioral tests in a C. elegans PLD mutant model. Interestingly, from our extensive characterization, the biometric analysis showed that PLD mutant worms are wider and have an increased volume in both fed and starved conditions when compared to N2 worms.Since the mechanism by which this phenotype arises is still elusive, we tested the hypothesis that lipid dysregulation could be involved. In line with that, we observed that PLD functional ablation leads to an increase in lipid droplets and cholesterol accumulation assessed by confocal imaging.Since we had previously observed that Aβ nematodes had decreased volume, we tested the impact of PLD ablation in this AD-like model. Remarkably, using PLDmut/Aβ animals, our results indicate that PLD functional ablation has a protective effect in motor and thrashing tasks, prevents susceptibility to a proconvulsivant drug (pentylenetetrazol), protects against deleterious effects of serotonin and, importantly, reverts the biometric phenotype in the Aβ animals, leading to the normalization of the worm body size.Overall, our data shows that PLD functional ablation has an important role in neurodegeneration. This is in accordance with previous reports showing that PLD2 genetic ablation ameliorates AD phenotypes in rodent models. The specificity of the phenotypes in our large-scale characterization sheds light in potential mechanisms contributing to AD pathogenesis.

Disclosures: **A.F. Bravo:** None. **J.D. Silva:** None. **R.B. Chan:** None. **G.D. Paolo:** None. **A.T. Castro:** None. **T.G. Oliveira:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.25/N12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5P20GM109025

Title: Effects of hyperglycemia in the APP/PS1 mouse model of Alzheimers disease

Authors: *J. W. KINNEY, A. MURTISHAW, A. SALAZAR, M. BOLTON, A. BOREN
Univ. of Nevada Las Vegas, Las Vegas, NV

Abstract: Alzheimer's disease (AD) is a debilitating neurodegenerative disorder that is characterized by memory deficits, neuronal loss, and death. Pathological hallmarks of the disorder include the accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau (ptau). An additional characteristic of AD includes a sustained inflammatory response (neuroinflammation) within the brain that has been demonstrated to promote and accelerate Aβ and ptau pathology. The cause of AD remains unknown but a number of risk factors exist for sporadic AD (sAD) that accounts for 95%-98% of all AD cases. Risk factors for sAD include genetic risk factors such as ApoE allele status or a missense mutation in TREM2 that results in altered inflammatory signaling. Several non-genetic risk factors for sAD also exist that include cardiovascular disease, obesity, and diabetes mellitus (DM). DM in particular is of interest as it induces hyperglycemia, insulin receptor resistance, and several other changes that impact the vasculature and inflammation. What remains to be elucidated is the exact mechanisms in DM that confers greater risk for developing AD, as well as what features of diabetes exacerbate AD pathology. In an effort to examine and unpack specific mechanisms that are altered in DM, and how they contribute to AD pathology we evaluated the effects of hyperglycemia in the APP/PS1 mouse model of AD versus wild-type (wt) controls. We have previously demonstrated that peripheral staggered administration of streptozotocin (stz) induces a sustained hyperglycemic state in wt mice that results in learning and memory deficits, increases in ptau, and increased activation of microglia. In the present study we evaluated if the hyperglycemia following stz treatment exacerbated learning and memory deficits, Aβ pathology, ptau, and inflammation in the well-established APP/PS1 mouse model of AD. We performed these investigations in both male and female mice to determine if hyperglycemia related changes differ based on sex. Our data indicate that several measures were altered by the combination of APP/PS1 and stz vs APP/PS1 alone, stz alone, and wt controls. This includes blood glucose levels that were elevated in the male APP/PS1 +stz group versus male APP/PS1 alone or male stz alone groups. Interestingly these effects differed in the female mice.

Disclosures: **J.W. Kinney:** None. **A. Murtishaw:** None. **A. Salazar:** None. **M. Bolton:** None. **A. Boren:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.26/O1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 5P20GM109025

Title: GABA specific changes in a mouse model of Alzheimer's disease

Authors: *A. J. BOREN, A. M. SALAZAR, A. M. MURTISHAW, M. M. BOLTON, J. W. KINNEY
Psychology, Univ. of Nevada Las Vegas, Las Vegas, NV

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with learning and memory deficits, neuronal loss, and eventually death. AD is characterized by the appearance of two key pathological features. These include the accumulation of Amyloid β plaques (Aβ) and hyperphosphorylated tau (ptau) that lead to neurofibrillary tangles. More recent evidence has demonstrated a sustained inflammatory response (neuroinflammation) contributes to both Aβ and ptau pathology. A number of mechanisms have been proposed that are responsible for impaired learning and memory, neuroinflammation, and progressive neuronal loss including alterations in several neurotransmitter systems. One neurotransmitter in particular that has been demonstrated to be altered in AD clinical populations and pre-clinical models is gamma amino butyric acid (GABA). GABA is the principle inhibitory neurotransmitter in the brain and has been demonstrated to play a vital role in several systems, including learning and memory and coordinated oscillations within the brain. As learning and memory deficits and altered population activity have been reported in clinical AD patients and animal models of AD a more careful examination of GABAergic changes in AD progression is needed.
In order to determine if changes in GABA related markers precede or co-occur with the onset of AD related deficits we evaluated several markers of GABAergic signaling in combination with behavioral measures and pathological markers of AD. Aβ plaques, Aβ oligomers, neuroinflammation, and behavior were measured at distinct time points (4, 6, and 10 months of age) in the APP/PS1 mouse model of AD versus aged matched wild-type controls. Our data indicate that at the time point that we observe learning and memory deficits in the APP/PS1 model and a clear presence of Aβ plaque formation that protein levels of GABA receptor subunits were significantly reduced in the hippocampus. Interestingly, protein levels of GAT3 and GAD-65 were elevated at this same time point. These data indicate that while there may be a reduction in GABA receptors, there is an increase in mechanisms associated with GABA

transport and production. These data support the need for further investigation of specific GABAergic changes in the progression of AD.

Disclosures: A.J. Boren: None. **A.M. Salazar:** None. **A.M. Murtishaw:** None. **M.M. Bolton:** None. **J.W. Kinney:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.27/O2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Neurodegenerative disease related neuropathology in the retina and olfactory bulb of transgenic rodent models

Authors: *B. HUTTER-PAIER, A. LOPEZ, V. NIEDERKOFLER, S. FLUNKERT, E. AUER, J. NEDDENS
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Abstract: Alzheimer´s disease (AD) is a progressive neurodegenerative disease that leads to neuropathology in the brain. Major hallmarks of the disease are deposition of beta-amyloid in neuritic plaques and formation of neurofibrillary tangles of hyperphosphorylated tau. Published research suggests associations between AD and functional impairments of sensory systems. Recently, the occurrence of Tau-mediated glaucoma has been reported, as well as AD protein-associated neuropathology in sensory systems. The current study is designed to analyze pathological changes in different transgenic rodent models of AD. Eyes and brains were collected from 6 and 12 months old APP rats, TAU rats and TMHT mice. Tissue was cryosectioned and analyzed for neuropathological features like Abeta and Tau expression, neuroinflammation using marker against activated microglia and astrogliosis and well as neurotransmitter level changes. For immunohistochemical analyses, uniform systematic random sets of cryosections were immunofluorescently labeled and retina and olfactory bulb quantitatively analyzed for 6E10, PHF-tau, tau, GFAP, Iba1, ChAT, GAD67 and TH expression. We will show data on age-associated pathology in the different rodent models. A major focus during interpretation of the data will be to find common pathology features that are associated with the expression of specific human proteins.

Disclosures: B. Hutter-Paier: None. **A. Lopez:** None. **V. Niederkofler:** None. **S. Flunkert:** None. **E. Auer:** None. **J. Neddens:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

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Program#/Poster#: 044.28/O3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH

CIHR

MSFHR

Title: Sleep and EEG power spectral analysis in three transgenic mouse models of AD: APP/PS1, 3xTgAD, and Tg2576

Authors: *B. A. KENT[1], S. M. STRITTMATTER[3], H. B. NYGAARD[2]
[1]Djavad Mowafaghian Ctr. for Brain Hlth., [2]NEUROLOGY, Univ. of British Columbia, Vancouver, BC, Canada; [3]CNNR Program, Yale Univ., New Haven, CT

Abstract: There is growing interest in the sleep disturbances associated with Alzheimer's disease (AD), particularly in regards to how sleep disruption contributes to disease pathogenesis and the utility of specific sleep changes as biomarkers for early detection of disease. However, little is known about how sleep architecture is affected in some of the most widely used mouse models, and the heterogeneity of methodology and analyses used in the existing studies makes comparisons difficult. Here, we analyze sleep and EEG power in three transgenic mouse models of AD, using identical methods to allow for a direct comparison between models. The goal was to assess the suitability of these mouse lines to model the broader neuronal network dysfunction measured by EEG in AD. APP/PS1, 3xTgAD, Tg2576, and littermate controls were analyzed by *in vivo* EEG recordings for analysis of sleep/wake time and EEG power. The EEG power spectrum showed no differences between genotypes in the 3xTgAD at 24 months of age, whereas the APP/PS1 mice at 7 months of age and the Tg2576 at 12 months of age showed reduced delta (0.5 – 4 Hz) and theta (4 – 8 Hz) power and higher alpha (8 -13 Hz) power compared to the littermate controls. These findings are similar to what has been identified by previous studies using mouse models of AD. However, it is unclear how the results compare to the EEG signature of patients with AD, who typically exhibit an increase in diffuse slow wave activity when awake, but also a reduction in slow wave sleep. Power spectrum analysis has been proposed as a useful, noninvasive neuroimaging tool for identifying prodromal impairment and early disease progression in MCI and AD, but more work is needed to identify the specific biomarkers.

Disclosures: B.A. Kent: None. **S.M. Strittmatter:** None. **H.B. Nygaard:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.29/O4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R15 AG039008

Title: Effects of prostacyclin signaling on Alzheimer's disease associated-pathologies

Authors: *T. WOMACK[1], C. VOLLERT[1], T. BECKETT[3], D. MAYERICH[2], M. P. MURPHY[4], J. L. ERIKSEN[1]
[1]Pharmacol. & Pharmaceut. Sci., [2]Electrical & Computer Engin., Univ. of Houston, Houston, TX; [3]Univ. of Kentucky, Lexington, KY; [4]Molecr & Cell. Biochemi, Univ. Kentucky, Lexington, KY

Abstract: Vascular pathologies are associated with accelerated neuronal damage and cognitive decline in Alzheimer’s disease (AD). We have conducted studies to address the effect of prostacyclin, a protective vasodilatory prostanoid, on the development of neurodegenerative pathologies in a mouse model of AD. The central hypothesis is that prostacyclin signaling may be protective at the site of the neurovasculature by influencing integral components of the blood brain barrier (BBB). Using behavioral studies, immunohistochemistry and biochemical assays, we are currently characterizing prostacyclin-mediated changes in behavior, amyloid deposition, and vascularization. Altered prostacyclin expression appears to protect against amyloid-associated declines in cognitive function, but also appear to alter neurovascular function.

Disclosures: T. Womack: None. **C. Vollert:** None. **T. Beckett:** None. **D. Mayerich:** None. **M.P. Murphy:** None. **J.L. Eriksen:** None.

Poster

044. APP: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 044.30/O5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Vascular amyloidosis, astrocytic endfeet, and blood brain barrier disruption

Authors: *W. A. MILLS, III[1], I. F. KIMBROUGH[2], H. W. SONTHEIMER[2]
[1]Translational Biology, Medicine, and Hlth., Virginia Tech. Carilion Res. Inst., Roanoke, VA; [2]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: The blood brain barrier (BBB) is a specialized brain endothelial structure that tightly regulates the bidirectional passage of components between the brain and blood. This is accomplished by the presence of tight junction and adherent junction proteins, along with numerous transport systems. Although initially induced by pericytes, tight junction proteins are both stabilized and maintained by astrocytes due to close physical contact of the astrocytic membrane with the blood vessel. In a previous study, our lab demonstrated that disruption of astrocytic contact due to invading glioma cells resulted in loss of the tight junction proteins zonula occludins-1 (ZO-1) and claudin-5, along with focal breaches in the BBB. We also recently demonstrated in the hAPPJ20 mouse model of familial Alzheimer Disease that vascular amyloid accumulates between the vessel and astrocytic endfoot, ultimately leading to endfoot separation. We now show that vascular amyloid deposits focally breach the BBB, as measured by leakage of low molecular weight blood tracer dyes imaged in live animals through a cranial window by multi-photon imaging. Immunohistochemical analysis of tissue from hAPPJ20 mice shows loss of the tight junction proteins ZO-1 and claudin-5, as well as the glucose transporter GLUT1. While this loss correlates with vascular amyloid accumulation and endfoot separation, whether the latter is causally involved in loss of tight junction proteins remains to be determined. It is possible that loss of tight junctions is secondary to impaired angiopoietin- src-suppressed kinase signaling, through which astrocytes are believed to promote tight junction expression. Alternatively, amyloid may exert toxicity directly to endothelial cells with endfoot retraction being a secondary event. Ongoing imaging studies will answer these questions.

Disclosures: W.A. Mills: None. **I.F. Kimbrough:** None. **H.W. Sontheimer:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.01/O6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Vetenskapsradet (Sweden) Grant 521-2014-3191

Title: Confronting alzheimer´s disease by targeting hypometabolism, insulin resistance and oxidative stress

Authors: *D. PAPADIA[1], A. I. IVANOV[2], M. Y. ZILBERTER[1], Y. ZILBERTER[2], A. FISAHN[1]

[1]NVS, Karolinska Institutet, Stockholm, Sweden; [2]Aix Marseille Univ. - INSERM, Marseille, France

Abstract: Alzheimer's disease (AD) is the most common form of dementia in the elderly, affecting more than 26 million people worldwide. The amyloid-beta hypothesis of AD focuses on accumulation of amyloid-β peptide (Aβ) as the main culprit for the neuronal changes in the brain, and postulates that Aβ accumulation results in neuronal dysfunction, synaptic loss and cognitive decline in patients. In addition abnormalities in metabolic pathways are observed very early in the pathogenesis of AD, manifested as reduced glucose metabolism, insulin resistance, neuronal energy deficit and oxidative stress. This highlights the importance of therapies targeting these processes. Our data show that the changes in resting membrane potential caused by acute application of Aβ are due to intracellular ATP depletion and that Aβ-induced reduction in neuronal glucose uptake is partlyresponsible for this. We tested whether pyruvate, as an alternative source of energy, and/or insulin, to counteract insulin resistance, could correct the metabolic deficiencies caused by Aβ and rescue downstream network dysfunction both at the cellular and network level. We show that pyruvate restores the reduced glucose utilization and completely prevents Aβ's toxic effect on neuronal excitability, while insulin has no effect on glucose utilization and is only partially effective in normalizing excitability. However, pyruvate and insulin have opposite effects at the synaptic level, At the network level, both pyruvate and insulin partially restore Aβ-disrupted gamma oscillations, but when applied together gamma oscillations power is rescued to control levels. Our data suggests non-overlapping therapeutic pathways of the two compounds and highlights the importance of a combination treatment using both compounds.
Based on our in vitro findings we used a treatment protocol combining chronic administration of pyruvate, insulin and Tempol (antioxidant). This treatment (PINTE) proved efficient in preventing cognitive decline in AD model mice (APP/PS1) and showed no side effects. Therefor we believe that our combinational treatment may represent a valid therapeutic approach for AD.

Disclosures: D. Papadia: None. **A.I. Ivanov:** None. **M.Y. Zilberter:** None. **Y. Zilberter:** None. **A. Fisahn:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.02/O7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 521-2014-3191

Title: Interference with amyloid-beta aggregation rescues degraded neuronal and synaptic parameters as well as network gamma oscillations in mouse hippocampus *In vitro*

Authors: *Y. ANDRADE-TALAVERA, SR, G. CHEN, J. JOHANSSON, A. FISAHN
Dept. of Neuroscience| NVS., Karolinska Institutet, Stockholm, Sweden

Abstract: The amyloid-β peptide (Aβ) is one of the main culprits for the myriad physiological changes seen during development and progression of Alzheimer's Disease (AD). The cognitive decline observed in AD goes hand-in-hand with a decrease of neuronal network rhythms such as gamma oscillations. This reduction consequently underlies the negative effects on learning, memory, perception and cognition typical of AD. The aim of our research was to investigate the effectiveness of compounds that interfere with the Aβ folding (Dec-DETA) and aggregation (Bri2) in the prevention of and rescue from Aβ toxic effects. The network and cellular mechanisms responsible for the rescue of the Aβ-degraded gamma oscillations are also elucidated. Recordings were performed in area CA3 of acute hippocampal slices from P14 - P35 mice. Local field potentials (LFPs) were recorded in an interface-type chamber or a submerged-type chamber (concomitant LFP/patch-clamp recordings). LFP gamma oscillations were elicited by applying kainic acid. In the submerged-type chamber recordings, the application of Dec-DETA or Bri2 increased the gamma power in slices pre-incubated 15 min with 50 nM Aβ. Dec-DETA is a designed ligand while Bri2 is a chaperone peptide highly expressed in human hippocampus. We proceeded to study the cellular and network mechanisms underlying the rescue by Bri2. In concomitant recordings the applicationof Aβ led to a degradation of gamma oscillations power and the subsequent application of Bri2 rescued gamma power back to control levels. Concomitantly to the LFP changes Aβ caused a widening of the firing window of pyramidal cells (PC), consistent with action potential (AP) desynchronization. Application of Bri2 tightens the firing window, which is equivalent to a higher AP synchronization. Gamma oscillations depend on a tightly regulated equilibrium between inhibition and excitation in the neuronal network. Recordings of EPSCs and IPSCs from PC in activated slices showed that Aβ application disrupts this balance while Bri2 application rescues the alterations observed in IPSCs frequency and EPSCs amplitude, thus counteracting the imbalance caused by Aβ in the network. The Bri2 used in our study comprises a mix of different conformations. We currently investigate whether peptide conformation could differently affect the effectiveness of Bri2 against Aβ toxicity. Recordings from slices pre-incubated with Aβ and different concentrationsof Bri2 monomers, dimers or oligomers show that Bri2 monomers are the most efficient Bri2 species at preventing Aβ degradation of gamma oscillations. Experiments directed to test the efficacy of Bri2 species in a rescue strategy are ongoing.

Disclosures: Y. Andrade-Talavera: None. **G. Chen:** None. **J. Johansson:** None. **A. Fisahn:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

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Program#/Poster#: 045.03/O8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IND-03-12

SNI34-2014

SNI163-2016

Title: Novel Indol derivatives as small molecule inhibitors of Amyloid aggregation

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Abstract: Alzheimer's disease (AD) is the most common form of dementia among the elderly and has become a leading public health problem worldwide. AD is characterized by progressive episodes of memory loss and language and reasoning problems that culminate in severe cognitive decline and death. According to the Alzheimer's association, AD is the 6th leading cause of death in United State. It also represents a great economic and psychological burden to caregivers and families.

The hallmarks of this neurodegenerative disorder are the presence of extracellular amyloid beta (Aβ) plaques, intracellular neurofibrillary tangles, and inflammation. Amyloid plaques are constituted of Aβ peptides originated by the cleavage of the amyloid precursor protein (APP). For the generation of Aβ, APP is cleavage by β-secretase (BACE1) and ɣ-secretase. These cleavages produce the $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides, being the $A\beta_{1-42}$ the principal component of senile plaques. This peptide is susceptible to self-aggregation forming insoluble and toxic species. Aβ first accumulates in oligomers, then in fibrils and finally into senile plaques.

Aβ has been pointed out as a key element for the development of AD. The amyloid hypothesis posits the accumulation of Aβ as the initial event that triggers the disease. Aβ is a crucial target for the treatment of AD, but to date, no effective treatment for the clearance of Aβ has been found.

Despite many efforts and incentives for the development of new drugs the rate of success is negligible. The need for new drugs to stop or slow AD progress is as important today as it was a few years ago. The organic synthesis of small molecules represents a feasible approach to generating potential therapeutic agents that are biologically active and safe.

We have identified by using the Thioflavin T (ThT) assay four new Hexahydropyrroloindoles (HPI) synthetic compounds able to inhibit the aggregation of $A\beta_{1-42}$. Kinetic of Aβ aggregation in the presence of compounds reveled that two compounds (1 and 3) present disaggregating capacity. Docking experiments suggested that the non-polar component of the interaction of compounds with Aβ, contributed favorable to the binding free energy of each complex. Modeling simulation confirmed compound 1 and 3 as disaggregated molecules. These compounds were able to rescue rat pheochromocytoma cells (PC 12) from the death induced by fibrils of Aβ.

This work adds to the efforts for the identification and characterization of new agents that may help to stop or delay the progression of AD.

Disclosures: **P. Llanes Fernandez:** None. **D. Doens:** None. **M. Carreira:** None. **M. Valdés Tresanco:** None. **O. Larionov:** None. **R. Lleonart:** None. **P. Valiente:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.04/O9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AHA Scientist Development Grant 15SDG22460003

grants from Mayo Clinic Center for Regenerative Medicine

Title: C3H/10T1/2 cell-derived pericytes eliminate brain amyloid-β in an LRP1-dependent manner

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Abstract: Pericytes are the major component of cerebrovasculature, which play a critical role in regulating blood-brain barrier integrity, angiogenesis, phagocytosis, cerebral blood flow, neuroinflammation responses, and stem cell activity. Pericytes also significantly contribute to amyloid-β (Aβ) metabolism in the brain. The disturbance of this pathway diminishes brain Aβ clearance, which is likely involved in the pathogenesis of Alzheimer’s disease (AD). Thus, to explore the ability of pericytes in Aβ clearance, the mouse mesenchymal stem cell line C3H/10T1/2 was differentiated into pericytes, and stereotaxically injected into the brain of amyloid AD model APP/PS1 mice at the age of 18-20 months. After 3 weeks of the injection, brain microcirculation in pericyte-injected hemisphere of the mice was significantly increased compared to contralateral hemisphere when measured by laser speckle contrast analysis technology. Importantly, immunohistochemical analysis demonstrated that pericyte implantation reduced Aβ deposition in the hippocampus of APP/PS1 mice. Consistently, we also found that levels of insoluble Aβ40 and Aβ42 were significantly lower in the hippocampus of pericyte-injected hemisphere than contralateral side by ELISA. Furthermore, since a major Aβ clearance receptor low density lipoprotein receptor-related protein 1 (LRP1) is abundantly expressed in pericytes, we examined the contribution of LRP1 to Aβ metabolism in C3H/10T1/2 cell-derived pericytes. When brain slices from aged APP/PS1 mice were incubated with pericytes for 24 hours, insoluble Aβ42 levels were significantly reduced in the brain slices. However, the ability of pericytes was diminished by LRP1 knockdown (KD). There was no significant difference between control and LRP1-KD pericytes in levels of major Aβ degrading enzymes, including insulin-degrading enzyme (IDE),

neprilysin, matrix metalloproteinase-2 (MMP2) and MMP9. These results indicate that LRP1 mediates the phagocytosis of brain Aβ aggregates in pericytes. Cell-based therapy through pericyte implantation may be a potential approach to develop novel interventions against AD.

Disclosures: **M. Tachibana:** None. **C. Liu:** None. **Y. Yamazaki:** None. **G. Bu:** None. **T. Kanekiyo:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.05/O10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CART Foundation

Title: The novel vaccine targeting oligomeric amyloid beta with immunomodulatory effects

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Abstract: Alzheimer’s disease is a group of diseases with similar neurological symptoms, and age is the accepted risk factor for these diseases. Most therapeutic approaches only target on a single factor, and not proper for long term use. Currently, there is no method can slow down or cure AD. Thus, there is a desperate need to develop and implement effective strategies for AD. Though many factors are proposed as cause of AD, Aβ accumulation and Tau phosphorylation are considered to be the major pathological factors. Thus, immunotherapy against pathological factors such as Aβ and Tau have emerged in the past 16 years and show great promise. AD patients are old subjects with deteriorated immune systems, so a normal vaccine strategy requires a strong adjuvants to stimulate or over prime the immune system. However, such adjuvants will lead to over activation of the immune system that induces an unwanted response. Practically, the best approach for effectively dealing with AD must be able to simultaneously target the pathological factor and address the impaired immune system for a longer period time. In the past 10 years, we have used Aβ peptide carrying a mutant T cell epitope as antigen to sensitized mouse bone marrow derived dendritic cells, and then use the preparation as vaccine to immunize APP/PS1 AD mouse model. Our vaccine can induce anti-Aβ antibody production and improve memory in mice. To target on the toxic isoform of Aβ, we use the preaggregated (aged) mutant peptide to sensitize DCs. The vaccine can induce isoform specific antibody response with significant immunomodulatory effect, and significantly improved memory tested by radial arm

water maze on APP/PS1 mouse model. The results of the study proves that our mutant Aβ sensitized DCs as vaccine can target on the oligomeric Aβ and fix the impaired immune system.

Disclosures: P. Pham: None. **X. Lin:** None. **Y. Hong:** None. **B. Brown:** None. **J. Cai:** None. **C. Cao:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The patent of this work has been licensed by Alzamend Neuro Inc..

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.06/P1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: American Nutrition Inc.

Cure Alzheimer Fund

Title: Effect of tocotrienols on GluA1 and amyloid beta protein: mevalonate pathway and beyond

Authors: A. M. MABB[1], H. MO[1], *W. XIA[2,3]
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Abstract: Neuropathological hallmarks of AD include the accumulation of amyloid beta protein (Abeta) containing neuritic plaques and Tau containing neurofibrillary tangles. Among therapeutic directions toward Alzheimer’s disease (AD), exploring noncanonical mechanisms in the amyloid synthesis pathway may reveal novel targets for intervention. Previous reports indicate a lower incidence of AD and cognitive impairment in populations exposed to higher levels of tocotrienols, but not tocopherols. Tocotrienols and statins perturb the mevalonate pathway by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which in turn decreases downstream levels of farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), intermediate products of the mevalonate pathway. In this study, we used primary hippocampal neurons to compare alterations in Abeta levels following addition of tocotrienols, statin, and farnesol. Neurons exposed to lovastatin or tocotrienol induced a dose-dependent reduction in Abeta protein, consistent with previous reports, whereas farnesol increased Abeta levels. Notably, immunohistochemical analysis revealed changes in expression of the excitatory alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subunit, GluA1, which represents a candidate pathway that could be altered, in addition to the

effect of statins and tocotrienols on HMG-CoA reductase. This is the first study linking statin, tocotrienol, and farnesol changes in amyloid metabolism to alterations in excitatory synaptic receptors. Our findings illustrate the mevalonate pathway as a potential target for Alzheimer therapeutics.

Disclosures: **A.M. Mabb:** None. **H. Mo:** 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.; American Nutrition Inc,. **W. Xia:** 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.; American Nutrition Inc..

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.07/P2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KHIDI grant HI14C1913

KHIDI grant HI15C

NRF grant NRF-2016R1E1A1A01941212

Title: High-throughput screening (HTS) of an FDA drug library for PDE inhibition: PKC-mediated effects of PDE-inhibiting drugs on lysosomal dysfunctions in *In vitro* models of Alzheimer’s disease

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Abstract: Lysosomal dysfunction is implicated as a contributing factor in brain aging as well as neurodegenerative diseases such as Alzheimer’s disease (AD). However, mechanisms leading to lysosomal dysfunction in these conditions are yet to be delineated. Protein kinase C (PKC) is enriched in neurons and serves diverse functions in metabolism, signaling, and plasticity. Brain PKC levels are affected in aging and Alzheimer’s disease. In AD, Aβ binds PKC and promotes its downregulation. Conversely, PKC activation reduces Aβ accumulation in *in vitro* models of AD, indicating that PKC may play a role in the pathogenesis of AD. The link between PKC and lysosomal function is not yet clear, but a recent study showed that PKC activation may lead to enhanced lysosomal function. Another possible regulator of lysosomal functions is cAMP, which

has been shown to upregulate lysosomal vATPase and normalize the “arrested autophagy” caused by presenilin-1 (PS1) mutation (Coffey EE et al. 2014. *Neurosci*.). Previously, we have shown that cilostazol, a PDE3 inhibitor clinically used as antiplatelet agent, reduces Aβ accumulation in cultured pericytes likely by increasing cAMP levels. Hence, in the present study, we screened ~800 FDA-approved drugs (SCREEN-WELL® FDA v. 2.0 Approved Drug Library, purchased from ENZO) for their PDE3-inhibiting activities. Effects on PDE3 activity were measured using PDELight™ HTS cAMP Phosphodiesterase Assay (LONZA). HTS revealed six drugs that potently inhibited PDE3. However, their effects were not selective for PDE3; all these also inhibited other PDE isoforms. Like cilostazol, these drugs re-acidified lysosomes to variable extents. In addition, these drugs as well as dibutyryl-cAMP (db-cAMP) substantially reduced the level of $p16^{ink4a}$, a marker for cell senescence, in cortical neurons. Of interest, these effects were blocked by the addition of pan-PKC inhibitor, GF109203X. Whereas PKC levels were substantially reduced in mAPP-PS1-expressing CHO cells (endogenous Aβ) as well as in cortical neurons exposed to Aβ (exogenous Aβ), they were restored by the treatment with PDE3 inhibitors or db-cAMP. These results suggest that PKC is one of the mediators of the cAMP effect on lysosomes. In the present study, we selected six FDA-approved drugs that showed broad-spectrum PDE inhibiting activities, and found that all six drugs reduced Aβ accumulation in cell models. These drugs may act by boosting degradative functions of lysosomes by enhancing their acidification in a PKC-dependent manner. Thus, future research would benefit from examining these drugs for alleviation of neuronal aging and neurodegeneration via restoration of lysosomal function.

Disclosures: **H. Kim:** None. **B. Seo:** None. **H. Park:** None. **J. Koh:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.08/P3

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The effects of Azuki extract on anti-Alzheimer's disease

Authors: *H. MIYAZAKI, Y. OKAMOTO, S. KATAYAMA, S. NAKAMURA, S. YONEKURA
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Abstract: Alzheimer’s disease (AD) is characterized by the formation of senile plaques in the brain, which contains fibrils composed of amyloid-β peptide (Aβ). This disease shows that detect Aβ aggregation at an early stage, cause symptoms such as memory defect, physical dysfunction and loss of language skills at a later stage. AD-drug, currently available, cannot cure or halt the progression of AD. Therefore, prevention in the preclinical stage is extremely important.

Previous reports indicated that Curcumin contained in turmeric suppressed the aggregation of Aβ, and reduced neuronal toxicity caused by Aβ. It is suggested that resveratrol contained in the grape peel may improve the cognitive function of AD patients. It is hypothesized that pigment compositions such as curcumin and resveratrol have a role of inhibiting against AD. Therefore, we try to identify the prevention compounds of AD from color-specific vegetables.
First, I tried to identify the vegetable extracts which suppress the aggregation of Aβ *in vitro* using Thioflavin assay. As a result, we found that Azuki extract suppressed the aggregation of Aβ. Next, in order to know whether Azuki extract had a role in prevention against AD *in vivo,* We examined by using AD model fly. This flies show that Aβ are aggregated in the brain, physical dysfunction and abnormal life span. We cultured the AD model flies with or without Azuki extract. We examined the expression level of Aβ in the brain using Western blot analysis. We found that Aβ accumulation was reduced by Azuki extract. Then, in order to test the effect of the Azuki extract on the physical dysfunction, we examined the climbing assay. In a normal diet group, AD model flies caused gradually physical dysfunctions by 30 days old. On the other hand, in Azuki extract diet group, AD model flies has normal physical function at 30 days old. Therefore, this result indicates that Azuki extract has a role in the suppression of physical dysfunction in AD model fly. Finally, in order to test the effect of Azuki extract for the life span of AD model fly, We examined the survival assay. In the average life span, Azuki extract diet group was 45 days, normal diet group was 33 days. Therefore, Azuki extract suppressed abnormal life span in AD model fly.
In this study, we showed that Azuki extract inhibited the aggregation of Aβ *in vitro*. Furthermore, using AD model fly, we found that Azuki extract suppressed accumulation of Aβ and symptoms such as physical dysfunction and abnormal life span. In the future work, we will identify the chemical compound derived from Azuki that have inhibitory effects on Aβ aggregation.

Disclosures: H. Miyazaki: None. **Y. Okamoto:** None. **S. Katayama:** None. **S. Nakamura:** None. **S. Yonekura:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.09/P4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Shoemaker Award for Neurodegenerative Research

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NIH Grant 1P01 DA028555

NIH Grant 2R37 NS36126

NIH Grant P01 NS31492

NIH Grant P20RR 15635

NIH Grant P30 MH062261

Title: The mixed-lineage kinase 3 inhibitor URMC-099 facilitates amyloid-β clearance in a mouse model of Alzheimer's disease

Authors: *T. KIYOTA[1], Y. LU[2], B. DYAVARSHETTY[2], M. NEMATI[2], G. ZHANG[2,4], H. A. GELBARD[5], H. E. GENDELMAN[2,3]
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Abstract: The URMC-099 is a brain penetrant small-molecule that potently inhibits mixed lineage kinase (MLK) type 3 (MLK3). MLKs are mitogen-activated protein kinase (MAPK) kinase kinases (MAPKKKs) that regulate the c-Jun amino-terminal kinase and p38 MAPK signaling cascades serving to coordinate a spectrum of immune processes that are disease-linked including those known operative in Alzheimer's Disease (AD). A recent study conducted in our laboratories demonstrated that URMC-099 facilitates Aβ uptake and degradation through endolysosomal protein trafficking with an inhibitory effect of pro-inflammatory responses in cultured murine microglia. Here we posit that URMC-099 could serve to affect beneficial improvement in Aβ neuropathogenesis by eliminating Aβ species in the diseased brain. To such end, we examined the therapeutic potential of the drug in APP/PS1 double transgenic mice used as a model of AD. We now report that URMC-099 attenuates β-amyloidosis and that this is linked to a changed microglia phenotype and protection of hippocampal neurogenesis impairment in the AD mice. Such a beneficial role for URMC-099 is highlighted by Aβ species removal in diseased brain tissue, and will be attractive as a therapeutic agent linked to a restoration of the brain's microenvironment.

Disclosures: **T. Kiyota:** None. **Y. Lu:** None. **B. Dyavarshetty:** None. **M. Nemati:** None. **G. Zhang:** None. **H.A. Gelbard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); URMC-099 is the proprietary asset of the University of Rochester Medical Center (US Patents: 8,846,909, 8,877,772, and 9,181,247, and international patents/applications). **H.E. Gendelman:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.10/P5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Vetenskapsradet (Sweden) Grant 521-2014-3191

Title: Trpv1 receptor activation rescues hippocampal neuron function and network gamma oscillations from amyloid-beta-induced impairment

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Abstract: Amyloid-β peptide (Aβ) is the main component of senile plaques in Alzheimer's Disease (AD) and seems to be responsible for the early cognitive deficits observed in AD patients. Clinical research has shown that cognition-relevant EEG patterns such as gamma oscillations are progressively disturbed with advancing cognitive impairment in AD patients. In the past we have demonstrated that Aβ can impair hippocampal neuron function and network gamma oscillations, and established relevant electrophysiological in vitro assays in mice. Recently, some studies have reported that the endocannabinoid anandamide, a known TrpV1 receptor agonist, can reverse hippocampal damage and memory impairment in rodents pretreated with Aβ and also protect neurons from Aβ-induced cytotoxic effects. We recently found that Aβ induces a degradation of gamma oscillations by desynchronization of action potential (AP) firing in CA3 pyramidal cells (PC) and impairment of the excitatory/inhibitory balance. Here we investigate a neuroprotective role of TrpV1 receptor activation against Aβ-induced degradation of hippocampal neuron function and gamma oscillations. We found that the TrpV1 receptor agonist capsaicin can rescue Aβ-induced degradation of hippocampal gamma oscillations by reversing the desynchronization of AP firing in CA3 PC. In contrast activation of CB1 or CB2 receptors had no beneficial effect on Aβ-induced degradation of hippocampal gamma oscillations. The mechanism underlying the protective capsaicin effect is TrpV1 receptor-dependent since the effect was absent in hippocampal slices from TrpV1 knockout mice or in the presence of the TrpV1 receptor antagonist capsazepine. Moreover, this mechanism seems to be related to the excitatory synaptic input since capsaicin treatment could reverse the Aβ-related impairment of EPSCs but not IPSCs. In conclusion, our findings suggest that TrpV1 activation may be a novel therapeutic approach in the fight against brain disorders associated with cognitive decline.

Disclosures: H. Balleza-Tapia: None. **S. Crux:** None. **Y. Andrade-Talavera:** None. **P. Dolz-Gaiton:** None. **D. Papadia:** None. **A. Fisahn:** None.

Poster

045. Amyloid-Beta as a Therapeutic Target

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 045.11/P6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Lundbeckfoundation

Danish MRC

Foundation to the Advancement of Medical Science

Veluxfoundation

Danish Alzheimer Research Foundation

Title: Effect of paroxetine on established amyloid pathology in the APPswe/PS1dE9 mouse model of Alzheimer's disease

Authors: *B. FINSEN[1], M. SIVASARAVANAPARAN[1], M. SEVERINO[1], L. Ø. OLESEN[2], A. METAXAS[1], E. BOUZINOVA[2], A. A. BABCOCK[1], J. B. HASSELSTRØM[3], J. B. GRAMSBERGEN[1], O. WIBORG[2]
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Abstract: A dysfunction of the serotonin system might contribute to aggravate amyloid pathology, which is a hallmark of Alzheimer’s disease. Recently, *prophylactic* treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram was found to reduce amyloid beta (Aβ) plaque load in the APPswe/PS1dE9 mouse model of Alzheimer’s disease. We therefore examined the effect of *therapeutic* treatment with the SSRI paroxetine on Aβ plaque load in aging, male APPswe/PS1dE9 mice. Initial characterization showed a 40% reduction in serotonin levels in the frontal cortex of APPswe/PS1dE9 mice at 18 months, compared to age-matched controls. Unbiased stereological estimation showed no difference in Aβ plaque load in neocortex of 12-month-old APPswe/PS1dE9 mice treated with paroxetine or vehicle for 3 months. Similarly, Aβ plaque load in the neocortex was comparable in 18-month-old APPswe/PS1dE9 mice treated with paroxetine or vehicle for 9 months. The lack of paroxetine effect was observed despite of therapeutic drug levels in plasma, which resulted in >80 % reduction in serotonin transporter binding levels in the neocortex and hippocampus of paroxetine treated compared to vehicle treated mice. In the hippocampus of the same mice we observed a small reduction in Aβ plaque load in mice, that were treated with a high dose of paroxetine, while mice, that were treated with a lower, but still therapeutic dose of paroxetine for 9 months, failed to show a

statistically significant reduction in Aβ plaque load. These results question whether chronic treatment with therapeutically relevant doses of SSRI is able to reduce the Aβ plaque load in the cerebral cortex of individuals with established Alzheimer's disease.

Disclosures: B. Finsen: None. **M. Sivasaravanaparan:** None. **M. Severino:** None. **L.Ø. Olesen:** None. **A. Metaxas:** None. **E. Bouzinova:** None. **A.A. Babcock:** None. **J.B. Hasselstrøm:** None. **J.B. Gramsbergen:** None. **O. Wiborg:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.01/P7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Bright focus A20152965

NIH UL1TR001108

NIH RO1 A6023012

Title: The role of TREM2 in regulating neurogenesis in a mouse model of tauopathy

Authors: *V. JADHAV[1], T. MCCRAY[1], G. XU[1], G. HENDRIK[1], C. SWINFORD[1], G. E. LANDRETH[2], B. T. LAMB[3], S. M. BEMILLER[4]
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Abstract: Alzheimer's disease (AD) is the most common form of dementia in adults. More than 35 million people worldwide are affected and over 5.5 million of these patients reside in the United States alone. AD, a major healthcare crisis currently has no available treatment strategies to slow or prevent the disease. Aging and genetic factors including recently identified mutations in *TREM2* (*Triggering Receptor Expressed on Myeloid Cells-2*), are the most significant risk factors associated with developing late-onset Alzheimer's disease. The main pathological hallmarks of Alzheimer's Disease are extracellular aggregation of amyloid beta (Aβ), intracellular aggregation of neuronal microtubule associated tau protein (tau) and cognitive decline.
Adult neurogenesis is a process of the maturation of functional neurons from precursor cells and occurs in specific brain regions across a lifespan. Alteration of neurogenesis is observed in various neurodegenerative diseases including AD. To elucidate the role of TREM2 in AD, we are examining how *Trem2*$^{-/-}$ affect neurogenesis in a humanized tauopathy model (hTau mice). We have previously demonstrated that hTau mice exhibit decreased neurogenesis as compared to

WT mice. Given the relationship between TREM2 and neurodegeneration we were interested in studying the role of TREM2 in neurogenesis. We examined neurogenesis in subventricular zone (SVZ), subgranular zone (SGZ) and olfactory lobes in aging hTau and hTau;*Trem2*$^{-/-}$ mice. We found aberrant neurogenesis in hTau;*Trem2*$^{-/-}$ as compared to hTau mice, which was most pronounced at 18 months, at which point pathology worsens and dramatic neurodegeneration occurs. Our study found that even when the compensatory increase in neurogenesis occurs at late timepoints in hTau;*Trem2*$^{-/-}$ mice, pathology still remains worse. Our findings will expand on an increasing body of literature defining the biological role of TREM2 in the brain, and in AD, and may represent a novel therapeutic target beneficial to AD patients.

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Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.02/P8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Bright Focus/A2015296S

DOD/W81XWH-14-1-0265

DOD/W81XWH-15-1-0267

Title: TREM2 deficiency results in exacerbated traumatic brain injury induced tau pathology in a mouse model of tauopathy

Authors: *N. CHOPRA[1], S. M. BEMILLER[1], N. KOKIKO-COCHRAN[2], K. ATSUKO[1], T. J. MCCRAY[1], G. XU[1], B. T. LAMB[1]
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Abstract: Alzheimer’s disease (AD) and traumatic brain injury (TBI) share a subset of common pathological hallmarks. In Chronic traumatic encephalopathy (CTE) patient’s pathologies related to, but not limited to, AD are observed, including the presence of extracellular amyloid beta (Aβ) accumulation and hyperphosphorylated and aggregated microtubule associated protein tau (MAPT; Tau). Moreover, patients who have received even a single mild traumatic brain injury are significantly predisposed to developing late onset Alzheimer’s Disease (LOAD) among other neurodegenerative disorders. Therefore, it is possible that central molecular components exist that unify these disorders. Triggering Receptor Expressed on Myeloid Cells-2 (TREM2) is found to be increased in ageing and disease states such as AD and TBI as well as in *in vivo* models of AD. Meanwhile, levels of phosphorylated tau are also found to be increased in both AD and TBI.

Herein, we studied the effects of TREM2 deletion in a humanized mouse model of tauopathy (hTau mice) before and after induction of TBI. TBI was administered using a cortical contusion model, and mice analyzed at 3 days post injury (DPI) and 120 DPI. Our preliminary data suggest that TREM2 is protective by reducing tau pathology and cognitive outcomes. Our results elucidate mechanisms related to both AD and TBI, as well as identify TREM2 as a potentially key player in the cascade of both neurodegenerative disorders.

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Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.03/P9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UDLAP Grant 145654

Title: Morphological changes in prefrontal cortex, dentate gyrus and hippocampus CA3 in 3RTAU13 transgenic mice model

Authors: *M. G. CANO RUIZ[1], R. A. VAZQUEZ-ROQUE[2], J. C. PENAGOS-CORZO[3], G. FLORES[2], E. MASLIAH[4]
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Abstract: Alzheimer's disease (AD) is the most common form of dementia. Several studies indicate that it will increase in the coming years. AD is characterized by a significant decline in memory and cognitive abilities. However, the mechanisms that are implicated are far from being understood. However, abnormal production of the TAU protein is suggested as a major cause. Hyperphosphorylation of TAU causes accumulation of filaments, which form neurofibrillary tangles in the neuronal body and dendrites, causing neuronal death. The objective of the present study was to corroborate the presence of morphological changes in a transgenic mice (tg) model of 3RTAU13.
Ten female tg mice, aged two and three months, of the C57BL/6 strain were used. Five of them formed the control group and five the experimental group. Tg mice expressing the human 3RTAU13 gene were generated by the reinsertion of the modified gene at the site of mutagenesis. Mice in the control group were treated with a vehicle, rather than the reinsertion of the modified gene. 10 neurons from prefrontal cortex layer three, dentate gyrus and hippocampus

CA3 were analyzed. Sholl analysis was used to quantify the dendritic arborization of each group. The statistical data ($p < 0.05$) confirm the alteration of morphological parameters in the analyzed regions. The 3RTAU13 model indicates a higher arborization and dendritic length in all regions of the hippocampus and prefrontal cortex.
The findings can be explained by neuronal compensation. In this sense, previous studies have shown deficits in neurogenic processes, as well as a decrease in neuronal signaling markers. The presence of abnormal results for a possible neuronal compensation in tg TAU models opens the door to the investigation of a mechanism to understand AD.

Disclosures: M.G. Cano Ruiz: None. **R.A. Vazquez-Roque:** None. **J.C. Penagos-Corzo:** None. **G. Flores:** None. **E. Masliah:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.04/P10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NINDS (NIH Grant R01NS073899)

Alzheimer’s Association (MCDN 15 370051)

Title: FKBP52 promotes tau aggregation

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Abstract: Tau is a microtubule stabilizing protein that aberrantly accumulates in neurodegenerative diseases known as tauopathies, the most common being Alzheimer’s disease. This abnormal tau aggregation contributes to neurotoxicity in the tauopathic brain. Molecular chaperones have been shown to regulate this process. Specifically, the Hsp90 co-chaperone, FK506- binding protein 52 (FKBP52), has been shown to interact with tau and stimulate the production of tau oligomers and fibrils. Since there is evidence that tau aggregation is neurotoxic, we hypothesized that increased expression of FKBP52 in the brain would exacerbate both oligomeric and insoluble tau formation leading to memory impairments a tau transgenic mouse model. To test this, bilateral hippocampal injections of FKBP52 AAV-9 or mCherry AAV-9 (control) were performed in rTg4510 and wild-type mice. After two months of the injections, electrophysiological recordings, hippocampal-dependent memory, and neuronal loss

were evaluated in these mice. In addition, we used mammalian cell culture models of tauopathy and primary murine neurons to further characterize the effect of FKBP52 in tau oligomerization and toxicity. Our findings suggest that FKBP52 stimulates tau pathogenesis.

Disclosures: M. Criado Marrero: None. **R. Blackburn:** None. **X. Wang:** None. **J. Baker:** None. **J. Koren:** None. **C.A. Dickey:** None. **L.J. Blair:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

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Program#/Poster#: 046.05/Q1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: France Alzheimer/Fondation de France (InsTauBrain project)

FHU VasCog

LabEx DISTALZ

Title: Tau, a new regulator of brain insulin signalling

Authors: *D. BLUM[1], A. LEBOUCHER[1], E. MARCINIAK[1], E. CARON[1], T. AHMED[2,3], A. TAILLEUX[4], J. DUMONT[5], T. ISSAD[6], E. GERHARDT[7], P. PAGESY[6], M. VILENO[1], C. BOURNONVILLE[1], M. HAMDANE[1], K. BANTUBUNGI[4], S. LANCEL[4], D. DEMEYER[1], E. VALLEZ[4], S. EDDARKAOUI[1], D. VIEAU[1], S. HUMEZ[1], E. FAIVRE[1], B. GRENIER-BOLEY[5], T. F. OUTEIRO[7], B. STAELS[4], P. AMOUYEL[5], D. BALSCHUN[2], L. BUÉE[1]
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Abstract: The molecular pathways underlying Tau pathology-induced cognitive deficits and neurodegeneration remain ill-defined. One prevalent hypothesis is that hyperphosphorylation, misfolding and fibrillization of Tau impair synaptic plasticity and cause degeneration. However, Tau pathology may also result in the loss of specific physiological Tau functions, which are largely unknown, but that could finally contribute to neuronal dysfunctions. In the present study, we demonstrate the ability of Tau to regulate brain insulin signalling. Our data notably demonstrate that Tau deletion leads 1) to an impaired synaptic and biochemical hippocampal response to insulin, caused by altered IRS-1 and PTEN activities and 2) to an impaired hypothalamic anorexigenic effect of insulin, associated to energy metabolism alterations. Consistently, we found that Tau haplotypes are associated with glycaemic traits in Humans. The

present data thus uncover a new Tau function in its ability to regulate brain response to insulin. This raises the hypothesis that the pathophysiological Tau loss-of-function could favor brain insulin resistance, which is instrumental for cognitive and metabolic impairments of AD patients.

Disclosures: **D. Blum:** None. **A. Leboucher:** None. **E. Marciniak:** None. **E. Caron:** None. **T. Ahmed:** None. **A. Tailleux:** None. **J. Dumont:** None. **T. Issad:** None. **E. Gerhardt:** None. **P. Pagesy:** None. **M. Vileno:** None. **C. Bournonville:** None. **M. Hamdane:** None. **K. Bantubungi:** None. **S. Lancel:** None. **D. Demeyer:** None. **E. Vallez:** None. **S. Eddarkaoui:** None. **D. Vieau:** None. **S. Humez:** None. **E. Faivre:** None. **B. Grenier-Boley:** None. **T.F. Outeiro:** None. **B. Staels:** None. **P. Amouyel:** None. **D. Balschun:** None. **L. Buée:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.06/Q2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NINDS Grant P01NS045260-01

NINDS Grant R01NS057128

NIMH Grant R15MH101703

Title: The tyrosine phosphatase PTPN13/FAP-1 links calpain-2, TBI and tau phosphorylation

Authors: *Y. WANG[1], R. A. HALL[2], M. LEE[1], X. BI[1], M. BAUDRY[1]
[1]Western Univ. of Hlth. Sci., Pomona, CA; [2]Dept Pharmacol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: Traumatic brain injury (TBI) increases the risk of developing Alzheimer's disease (AD) and other types of dementia years or even decades later. Tau hyperphosphorylation is a hallmark of both AD and TBI. While many kinases and phosphatases have been shown to regulate tau phosphorylation at multiple sites, inhibitors of these enzymes have failed to be developed into therapeutic drugs, largely due to the multiple roles of those enzymes in many signaling pathways. Thus, alternative strategies are needed for targeting tau phosphorylation. The calcium-dependent protease calpain has been implicated in both TBI and AD. We recently discovered that the two major calpain isoforms in the brain, calpain-1 and calpain-2, play opposite functions in synaptic plasticity and neuronal survival/death, which may be related to the different PDZ domain binding motifs in their C-termini. Here we identify the tyrosine phosphatase PTPN13/FAP-1 as a key PDZ binding partner of calpain-2. Furthermore, PTPN13 is cleaved by calpain-2, which inactivates its phosphatase activity and generates stable breakdown products (P13BPs). We also identified the protein kinase c-Abl as a major target of PTPN13, and

found that calpain-2-mediated PTPN13 truncation resulted in c-Abl activation and tau tyrosine phosphorylation. Following TBI, calpain-2 activation cleaved PTPN13, activated c-Abl and triggered tau phosphorylation and tau oligomer formation, as post-TBI injection of a calpain-2 selective inhibitor inhibited the activation of this pathway as well as the accumulation of tau oligomers. In addition, P13BPs were found to be significantly elevated in post-mortem AD brains. Thus, the calpain-2/PTPN13/c-Abl pathway provides a direct link between calpain-2 activation and abnormal tau phosphorylation, which may promote tau oligomer formation and accelerate the development of AD pathology after repeated concussions or TBI. Our results also suggest that P13BPs could represent potential biomarkers for the diagnosis of TBI or tauopathy, including AD.

Disclosures: Y. Wang: None. **R.A. Hall:** None. **M. Lee:** None. **X. Bi:** None. **M. Baudry:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.07/Q3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSF Grant 1533763

Title: Neuroprotective effects of cembranoids in *Caenorhabditis elegans*

Authors: *K. A. BASKERVILLE, K. JACKSON
Biol., Lincoln Univ., Lincoln University, PA

Abstract: A loss of acetylcholine has long been implicated in the degeneration and memory loss seen in Alzheimer’s disease, and, as we have shown, is also observed in normal aging. We have recently crossed an Alzheimer’s disease (AD) *C. elegans* model (*pha-1*(e2123) III; hdEx81) with a mutated cholinergic (*cha-1*) strain of *C. elegans*. Our *C. elegans* AD-cholinergic cross could provide further clues of the role of acetylcholine in AD and enable us to identify agents that could protect cholinergic neurons from cell death. One intriguing neuroprotective agent is the cembranoids. Cembranoids protect against neurodegenration in Planaria and rodents and appear to act at nicotinic acetylcholine receptors. We hypothesize that cembranoids may protect cholinergic neurons in *C. elegans* from degenerative changes during the aging process. We have exposed the *C. elegans* strains to hydrogen peroxide and find that the *cha-1* mutant strains are sensitive to hydrogen peroxide treatment. Learning behaviors were assessed using a habituation protocol. Cembranoids appear to protect the C. elegans from oxidative damage. We are investigating the mechanisms of the neuroprotection of the cembranoids. Thus, cembranoids may be a potential neuroprotective agent to rescue neurodegeneration in *C. elegans*.

Disclosures: **K.A. Baskerville:** None. **K. Jackson:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.08/Q4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Characterization of tau expressing P301S mouse model for tauopathy - Longitudinal Brain Structural and Metabolic Profile

Authors: J. T. PUOLIVALI, K. LEHTIMÄKI, T. HUHTALA, J. RYTKÖNEN, *A. J. NURMI
Charles River Discovery, Kuopio, Finland

Abstract: P301S (B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J) mouse is a widely used tauopathy model. Majority of the work described for the model focuses on the brain pathology after 6 months of age, when there has been reported more prominent tau pathology, neuronal cell loss and atrophy. As the early development of tauopathy, behavioral phenotype and both structural and metabolic profile of the brain in P301S (TG) model have not been well characterized, we sought to examine longitudinal phenotype of this model with anatomical imaging, 1H-spectroscopy, metabolic imaging (PET) and behavioral features, and comparing them to aged matched wild type (WT) mice. Wild-type (WT) and P301S mice were studied starting at age of 2 months and followed up until age of 8-10 months. Behavioral battery included motor assays and selected cognitive assays. For the brain structural analysis, we applied T2-MRI to evaluate whole brain, cortical, hippocampal, striatal and ventricle volumes over time between WT and TG mice. In addition, we performed 1H-MRS to examine metabolic profiles over time on corresponding time-points. Furthermore, PET imaging was applied to evaluate metabolic activity as well as in vivo inflammation. We report longitudinal characterization of P301S mouse line. Data indicates that P301S model has a small but clear brain structural and metabolic phenotype as evidenced by T2-MRI and 1H-MRS when compared to WT mice already from two months of age. P301S mice are also cognitively impaired in RAWM and CFC tests compared to corresponding wild type mice. Phenotyping with translational tools provides compelling readouts for drug development.

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Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.09/Q5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Alterations of dendritic morphology in tau transgenic mice

Authors: *D. BORGMANN[1], K. MORCINEK[1], B. DENGLER[1], L. MÜLLER THOMSEN[1], J. GOETZ[2], H. SCHRÖDER[1], S. HUGGENBERGER[1]
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Abstract: Protein tau is the pathogenetic key driver in a group of devastating neurodegenerative diseases known as tauopathies, comprising Pick's disease and Alzheimer's disease. During the development of these conditions, pathological hyperphosphorylation of tau protein leads to its reduced binding to microtubular filaments, resulting in aggregation of neurofibrillary tangles and destabilization of dendritic compartments. Altered morphology of pyramidal neurons in the Cornu Ammonis 1 (CA1) region is supposed to lead to functional changes and impairment of hippocampal circuitry. This may contribute to the development of symptoms found in tauopathies, like memory impairment, cognitive decline and parkinsonism. To evaluate the impact of hyperphosphorylated tau on hippocampal function, we histopathologically investigated CA1 regions of Golgi stained brain sections from pR5 mice, carrying the P301L mutation. Dendritic morphology and spine density was assessed with Sholl analysis or semiautomatically, respectively, while hippocampal CA1 volume was estimated stereologically. Findings were compared between pR5 mice and non-transgenic littermates. We found a significant decrease in dendritic length of CA1 neurons ($p=0.033$) which resulted from a highly significant decrease in the length of the distal compartment of the apical dendrite (apical tuft) in senescent pR5 mice ($p<0.001$). Interestingly, apical tuft dendritic spine density appeared unchanged between genotypes. However, in transgenic pR5 mice spine density was positively correlated with the spatial expansion of the dendritic tree ($r=0.50$, $p=0.001$), the number of secondary apical branches ($r=0.66$, $p<0.001$), and the number of primary branches originating from the soma ($r=0.32$, $p=0.036$), as well as the length of proximal branches of the apical dendritic tree ($r=0.58$, $p<0.001$).We showed that the P301L mutation leads to morphological changes of CA1 neurons in senescent pR5 mice. The number of synapses reflected by dendritic spine density was not altered in apical tuft regions of transgenic mice per se. The correlation of spine density to the degree of morphological changes in transgenic pR5 mice, however, points to the potential existence of affected and un-affected neuron groups.

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Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.10/Q6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Merck & Co

Title: Biochemical and histological characterization of a transgenic rat that expresses a dimerization-prone construct of human tau

Authors: *T. W. ROSAHL[1], M. K. SCHULTZ, JR[2], X. TIAN[3], M. COSDEN[3], J. MAJERCAK[3], J. SCHACHTER[3]
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Abstract: Pathological hyperphosphorylation, misfolding, and aggregation of tau are components of many neurodegenerative disorders, such as Alzheimer's disease. We have developed and characterized a transgenic rat model that expresses a construct of human tau prone to dimerization. The construct consists of two copies of full-length human tau, expressed as a single protein that we refer to as Tandem Repeat Tau (TRT). Expression of TRT in HEK293 cells results in formation of soluble, hyperphosphorylated, high molecular weight tau oligomers. To assess whether the TRT construct would generate AD-like tau pathology in brain, we created a transgenic rat that expresses TRT under the control of the Camk2a promotor. We collected brains from these rats at 18, 26, and 43 weeks of age, and used biochemical and histological evaluations to compare markers of tauopathy between heterozygous, homozygous, and wild type rats (HOM, HET, WT). Rats that were homozygous and heterozygous for the TRT transgene displayed expression in olfactory, cortical, and hippocampal neurons, as verified by staining with the HT7 monoclonal TAU antibody. These areas also stained positive for the TAU phospho (Ser202, Thr205) specific antibody AT8, a marker for pathologically phosphorylated tau in both HET and HOM rats, with HOM rats showing a more robust profile than HET rats. Misfolded tau, identified with MC1, was only seen in HOM rats. Hyperphosphorylation of tau at several epitopes was confirmed by Western blot and immunoassays. This transgenic rat model will support studies evaluating the role of tau hyperphosphorylation in the initiation and progression of tau pathology.

Disclosures: **T.W. Rosahl:** A. Employment/Salary (full or part-time):; Merck & Co. **M.K. Schultz:** A. Employment/Salary (full or part-time):; Merck & Co. **X. Tian:** A.

Employment/Salary (full or part-time):; Merck & co. **M. Cosden:** A. Employment/Salary (full or part-time):; Merck & Co. **J. Majercak:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim. **J. Schachter:** A. Employment/Salary (full or part-time):; Merck & Co.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

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Program#/Poster#: 046.11/Q7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG051390

NIH U54 NS100717

NIH R01 AG051390

Title: Investigating the role of TREM2 in microglial motility, tau pathology, and tau-associated deficits

Authors: *F. SAYED[1,2], D. LE[3], Y. ZHOU[3], Y. LI[3], A. HAUDUC[3,4], F. GAO[5], B. DJUKIC[3], V. RAFALSKI[3], D. DAVALOS[3], K. AKASSOGLOU[3,2], G. COPPOLA[5], L. GAN[3,2]
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Abstract: Alzheimer's disease (AD), the most common form of dementia, is characterized by the abnormal accumulation of amyloid plaques and hyperphosphorylated tau aggregates. In addition, postmortem brain tissue from AD patients exhibit microgliosis, or increased microglial activation and number. Microglia are the immune cells of the central nervous system that clear debris, phagocytose pathogens, and mediate inflammation. Whether microgliosis in AD brain tissue is a cause or consequence of the disease remains unclear. The recent genetic implication of a microglial gene, Triggering Receptor Expressed on Myeloid Cells 2 (*TREM2*), in sporadic AD suggests a causal role for microglia in this disease. Carriers of a rare missense variant in *TREM2*, R47H, are at an increased risk for developing late-onset AD with an odds ratio of 2.8-3.45. *TREM2* is the strongest immune gene-specific risk factor discovered thus far. Moreover, patients carrying this variant have more phosphorylated tau than non-carrier AD patients, suggesting a relationship between *TREM2* and tau. *TREM2* encodes a transmembrane receptor, TREM2. In the brain, this receptor is only expressed by microglia. Microgliosis can promote tau phosphorylation and aggregation. Whether TREM2 plays a role in microglial regulation of tau pathology is a major gap in the field.
TREM2 R47H is posited to be a loss-of-function variant, which would

induce*TREM2* haplodeficiency. To characterize the effect of *TREM2* haplodeficiency on tau pathology, we generated a tauopathy mouse model expressing human mutant tau (*MAPT*^{P301S}; PS19 mouse model) with one or both copies of *TREM2*. We found that *MAPT*^{P301S};*TREM2*+/- mice show an increase in tau aggregates, suggesting a worsening of tau pathology in mice with reduced TREM2 expression. Using *in vivo* two photon microscopy, we found that *TREM2*+/- microglia are slower to respond to acute tissue injury. Future experiments will address whether this impaired chemotactic response in *TREM2*+/- microglia underlies the increase in tau pathology, and the consequences of *TREM2* R47H on tau pathology, microglial motility, and neuronal function using wild-type and R47H human *TREM2* knock-in mice.

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Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

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Program#/Poster#: 046.12/Q8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IMSD NIH R25GM62232

Title: Expression of human tau protein in *Caenorhabditis elegans* as a model for neurodegeneration in Alzheimer's disease

Authors: *K. B. MORALES[1], M. BIRRER[2], T. C. GAMBLIN[2], B. D. ACKLEY[2]
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Abstract: More than 5 million Americans over the age of 65 have Alzheimer’s disease (11% of that population). Yet, we still have an incomplete understanding of the underlying mechanisms of neuronal cell death in this disease. Strong evidence implicates the accumulation of aggregated tau protein into neurofibrillary tangles as a likely cause of neuronal dysfunction in Alzheimer’s disease. The observations in support of this are: the microtubule-associated protein tau has a known function, tau aggregates are found in other neurodegenerative diseases in the absence of other pathological structures, and the location and amount of pathological aggregation of tau correlates with the type and severity of human dementia. The mechanisms by which tau aggregates result in altered neuronal function are controversial and poorly understood, given the difficulties associated with modeling tau aggregation and neurodegeneration in animal models. To address this problem, we are attempting to generate multiple lines of transgenic animals expressing different variants of tau to better understand its aggregation and the subsequent downstream events leading to increased toxicity. We have chosen to employ the nematode worm

Caenorhabditis elegans as our model of choice as it is a powerful genetic model with a well-characterized nervous system, allowing for the study of the effects of human proteins in neurodegenerative disorders. We have produced multiple *C. elegans* transgenic lines expressing variants of human tau protein in neurons to compare their effects on proper neuronal function. Worms with mutations in htau40 (the largest human tau protein isoform) display a decreased lifespan, and progressively have difficulty moving as they age. Additionally, when expressed specifically in GABAergic motorneurons, mutant htau40 leads to a decrease in the number of neuron synapses during aging, prior to any observed neuron degeneration. Together, these results indicate the potential of *C. elegans* to serve as a model to explore tau aggregation and its subsequent effects on neuronal and synaptic homeostasis.

Disclosures: K.B. Morales: None. **M. Birrer:** None. **T.C. Gamblin:** None. **B.D. Ackley:** None.

Poster

046. Tau: Animal and Cellular Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG042178

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Garrison Family Foundation

Title: A partial loss of dynamin-related protein 1 enhances dendritic spines, reduces fragmented mitochondria and increases hippocampal based cognitive function in mutant Tau mice

Authors: *R. KANDIMALLA[1], M. MANCZAK[2], X. YIN[2], C.-S. KURUVA[2], M. VIJAYAN[2], S. KUMAR[2], P.-H. REDDY[2]
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Abstract: Increasing evidence suggests that phosphorylated tau (pTau) and mitochondrial abnormalities are involved in the loss of synapses, defective axonal transport and cognitive decline, in patients with Alzheimer’s disease (AD). We recently found increased levels of Drp1 and pTau and physical interaction between Drp1 and pTau, leading to excessive mitochondrial fragmentation, defective mitochondrial function and synaptic damage in AD neurons (Manczak and Reddy *Hum Mol Genet* 21, 2538-2547: 2012). Based on these observations, we hypothesized that a partial reduction of Drp1 inhibits Drp1-pTau interactions and protects neurons from pTau-induced mitochondrial and synaptic toxicities, and maintains neuronal function in AD

progression. To test our hypothesis, we created double mutant (Drp1+/xTau (P301L)) mice and studied the protective effects of reduced Drp1 in Tau in 6-, 12- and 20-month-old Drp1+/-xTau mice. In our recent 6-months old TauXDrp1 mice, we reported decreased mRNA expressions and protein levels of fission, and increased levels of fusion, biogenesis and synaptic genes relative to Tau mice (Kandimalla et al., *Hum Mol Genet*. 25, 4881-4897: 2016). Using molecular, biochemical, Golgi-cox staining and transmission electron microscopy studies, we investigated mRNA, protein levels of mitochondrial and synaptic genes, dendritic spines, mitochondrial number and morphology and Morris Water Maze based cognitive behavior in 12-month-old Drp1+/-xTau mice relative to age-matched Tau mice. We found significantly increased dendritic spines, significantly reduced fragmented and structurally damaged mitochondria and reduced mRNA and protein levels of fission genes and increased levels of fusion and synaptic genes in the brains of 12-month-old Drp1+/-xTau mice relative to age-matched Tau mice. Importantly, we also found ameliorated cognitive deficits in 12-month-old Drp1+/-xTau mice relative to age-matched Tau mice. These observations strongly suggest that reduced Drp1 is beneficial to AD neurons and may have a therapeutic value to AD patients.

Disclosures: **R. Kandimalla:** A. Employment/Salary (full or part-time):; Full, Garrison Institute on Aging & Pharmacology-Neuroscience, Texas Tech University health Sciences Center. **M. Manczak:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **X. Yin:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **C. Kuruva:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **M. Vijayan:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **S. Kumar:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center. **P. Reddy:** A. Employment/Salary (full or part-time):; Full, Texas Tech University Health Sciences Center.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.14/Q10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: LECMA, grant 2016/2017

Title: Development of AAV-based model of tauopathy to study the propagation of pathological forms of Tau

Authors: *A.-P. BEMELMANS, A. VAUTHENY, L. STIMMER, G. AUREGAN, C. JOSÉPHINE, M.-C. GAILLARD, P. HANTRAYE, K. CAMBON
CEA, Fontenay Aux Roses, France

Abstract: On the anatomopathologic level, Alzheimer's disease is characterized by two types of lesions present in the brains of patients: extracellular senile plaques composed mainly of A-beta peptides, and tangles which are intra-neuronal aggregates of Tau proteins. The latter evolve in the brains of patients following a characteristic spatio-temporal sequence which has been defined by the Braak stages and correlates closely with the intensity of the cognitive symptoms. The physiological role of the Tau protein is to stabilize the microtubule cytoskeleton in the axonal compartment of the neurons. In pathological conditions, Tau is hyperphosphorylated and acquires an abnormal conformation which leads to its aggregation in neurofibrillary degenerations. It is generally accepted that this spread of tauopathy in the brains of patients is due to an abnormal transmission of Tau between connected neurons, however the mechanism of neuron to neuron transmission is not clearly understood. It is therefore crucial to elaborate relevant experimental tools to study the mechanisms of this spread and to test therapeutic strategies to stop it. We developed a model of tauopathy based on overexpression using AAV vectors of different forms of human 1N4R Tau protein, normal or mutant, with different properties of hyperphosphorylation and aggregation. The injection of these vectors into the CA1 layer of the hippocampus in rodents demonstrates that Tau neurotoxicity for transduced pyramidal neurons is inversely correlated with its aggregation, reinforcing the thesis that soluble Tau oligomers are more toxic than insoluble aggregated forms. Our model, by its focal expression of the Tau protein, is an ideal experimental paradigm to study the mechanisms of the propagation of pathological forms. By injecting the vector into the medial entorhinal cortex, it is possible to observe Tau overexpression in this structure as well as in the axons of the perforant pathway and to study the propagation of pathological forms in the target neurons at the level of the hippocampus. We will use this injection route to determine, through our vectors expressing different forms of Tau, whether hyperphosphorylation and / or Tau aggregation play a role in the propagation of its pathological forms between interconnected neurons. Tau propagation can also be studied using in vitro models. To that aim, we transduced primary neurons from mouse cortex. Our preliminary results show that it leads to Tau hyperphosphorylation and aggregation as soon as 8 days post-transduction.

Disclosures: **A. Bemelmans:** None. **A. Vautheny:** None. **L. Stimmer:** None. **G. Auregan:** None. **C. Joséphine:** None. **M. Gaillard:** None. **P. Hantraye:** None. **K. Cambon:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.15/Q11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: La Marató de TV3 Fundation 20143330-31

Spanish Ministry of Economy, Industry and Competitiveness SAF2016-76340-R

Title: Reelin reduces Tau phosphorylation and reverts phospho-Tau somatodendritic missorting in mouse models of Tauopathy

Authors: *D. ROSSI[1,2,3], A. GRUART[4], J. AVILA[3,5], J. DELGADO-GARCIA[4], E. SORIANO[1,2,3], L. PUJADAS[1,2,3]
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Abstract: Reelin is an extracellular matrix protein that is crucial for adult brain plasticity and that has been demonstrated to be protective against amyloid-β (Aβ) pathology in Alzheimer's Disease (AD), reducing plaque deposition and synaptic loss, and preventing cognitive decline. Here we explore the involvement of Reelin in AD-related Tau pathology, the other main hallmark of the disease. One of the initial events of Tauopathy is the missorting of axonal proteins, such as neurofilaments and Tau, to the somatodendritic compartment. In primary hippocampal neurons we explored the impact of Reelin on Aβ-induced redistribution of axonal proteins to dendrites. In parallel we found that Reelin reverts *in vivo* the toxic somatodendritic localization of phosphorylated Tau in dentate granule cells of hippocampus in a model of overexpression of Glycogen Synthase Kinase-3β (GSK-3β), one of the main kinases for Tau protein. In the same transgenic line, we found that Reelin overexpression reduces the levels of GSK-3β-dependent Tau phosphorylation on AD-related epitopes. We further confirmed the Reelin-mediated reduction of Tau phosphorylation in another model of Tauopathy overexpressing a mutated form of human Tau linked to dementia (VLW mouse model), with effects on both human and mouse Tau. Finally, we also explored whether Reelin overexpression in tauopathy models modulates cognitive performances of adult mice. Our data indicate that Reelin, already described as protective against Aβ pathology, is also antagonizing Tau pathology, strengthening its potential as a therapeutic target at the crossway of the two key hallmarks of the disease.

Disclosures: D. Rossi: None. **A. Gruart:** None. **J. Avila:** None. **J. Delgado-Garcia:** None. **E. Soriano:** None. **L. Pujadas:** None.

Poster

046. Tau: Animal and Cellular Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 046.16/Q12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Natural Science Foundation of China (31271123)

Title: The PI3K signaling regulates tau phosphorylation and neuron survival

Authors: *G. CHEN, C. XU, J. HOU, L. WANG, S. CHENG
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Abstract: Impairment in the PI3K-PDK1-Akt signaling has recently been observed in Alzheimer's disease. However, it remained unknown exactly what roles this pathway may play in neurodegenerative processes. To address this question, we generated viable *Akt* three-isoform conditional knockout (cTKO) and *PDK1* cKO mice. We demonstrated that both *Akt* cTKO and *PDK1* cKO mice exhibit elevated levels of phosphorylated tau (p-tau). To investigate the underlying mechanisms, we examined activities for several major tau kinases including PKA, GSK3β, Cdk5 and Erk1/2. Levels of p-VASP or p-CREB are increased in *Akt* cTKO and *PDK1* cKO mice, suggestive of enhanced PKA activity. Levels of p-GSK3β^{Ser9} are increased and those of p25 are decreased in *Akt* cTKO and *PDK1* cKO mice, indicating decreased activities for GSK3β and Cdk5. Levels of p-Erk1/2 are reduced in *PDK1* cKO mice but unchanged in *Akt* cTKO mice. Therefore, changes on p-tau levels in *Akt* cTKO and *PDK1* cKO mice are a combined effect caused by altered activities of tau kinases. On the other hand, we found that *Akt* cTKO and *PDK1* cKO mice do not show significant changes on levels of α-, β- and γ-secretases. Consistent with this, levels of soluble APPα fragment and APP C-terminal fragment (CTF) are not increased and no amyloid deposition is found in *Akt* cTKO and *PDK1* cKO mice. Therefore, activities for APP-cleavage enzymes are not altered. We further demonstrated that there are remarkable reductions on the total cortical number in *Akt* cTKO and *PDK1* cKO mice, indicating massive neuron loss. Finally, increased number of TUNEL positive cells has been observed in mutant mice, suggesting that the PI3K signaling may control neuron survival through an apoptotic mechanism. Overall, our data highlight profound roles of the PI3K signaling in the pathogenesis of neurodegenerative disease.

Disclosures: G. Chen: None. **C. Xu:** None. **J. Hou:** None. **L. Wang:** None. **S. Cheng:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.01/R1

Topic: C.03. Parkinson's Disease

Title: Enhancement of dorsolateral prefrontal cortical neuronal firing in monkeys performing a working memory task by a novel non-catechol dopamine D1 receptor agonist

Authors: *M. WANG[1], V. C. GALVIN[2], S. YANG[3], R. KOZAK[4], D. GRAY[5], K. FONSECA[6], A. F. ARNSTEN[7]
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[4]Neurosci. Res. Unit, Pfizer, Cambridge, MA; [5]Pfizer, Groton, MA; [6]Pfizer, Cambridge, MA; [7]Yale Univ. Sch. Med., New Haven, CT

Abstract: Dopamine D1 receptor (D1R) agonists have been considered a potential treatment for dorsolateral prefrontal cortical (dlPFC) cognitive deficits in schizophrenia. For example, D1R stimulation may lead to phosphorylation of NMDA receptors that maintains them within the post-synaptic density. However, treatment has been hampered by the inverted U dose-response of available D1R agonists, where higher doses have been shown to suppress dlPFC neuronal firing, reduce neuronal representation, and cause D1R internalization. In this study, we are testing a novel, non-catechol D1R agonist, PF-3628, in aged rhesus monkeys with naturally-occurring depletion of dopamine and reductions in dlPFC neuronal firing during a spatial working memory task. We iontophoretically applied the novel D1R agonist onto Delay cells in the dlPFC of primates engaged in the oculomotor delayed response task, and compared results to a traditional D1R agonist, SKF81297. We found that iontophoresis of PF-3628 at 10-25nA strongly enhanced the delay-related firing of dlPFC neurons, and also enhanced their spatial tuning. These effects of PF-3628 were strikingly different from traditional D1R agonists, which sculpt and suppress dlPFC neuronal firing. These results suggest that novel, non-catechol D1R agonists may provide promise as a novel treatment strategy for dlPFC cognitive deficits in mental illness.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.02/R2

Topic: C.03. Parkinson’s Disease

Title: D1-selective partial agonist PF-9571 has robust and sustained efficacy, and did not induce dyskinesias, in the MPTP nonhuman primate model of Parkinson’s motor symptoms after repeat dosing

Authors: *D. GRAY[1], R. KOZAK[2], W. LIU[1], K. FONSECA[1], E. BEZARD[3]
[2]Neurosci. Res. Unit, [1]Pfizer, Cambridge, MA; [3]Inst. of Neurodegenerative Dis., Bordeaux, France

Abstract: Insufficient activation of striatal dopamine receptors underlies the cardinal motor deficits in Parkinson’s disease (PD). Increasing activation of D1R’s has been a longstanding goal for control of PD motor symptoms. D1R selective agents such as A-77636 and dihydrexidine have demonstrated robust single dose efficacy in the translatable MPTP PD motor symptom

model (Taylor, 1991; Pearce, 1999) however, ligands with suitable pharmacokinetics for robust clinical investigation have proved elusive. Furthermore, a handful of preclinical reports emerged suggesting that D1R agonist ligands may have response tachyphylaxsis (Blanchet, 1996) and potential for increased induction of dyskinesias (Westin, 2007; Darmopil, 2009). This work reports preclinical assessment of PF-9751, a selective D1R non-catechol partial agonist from a new chemical class with improved pharmacokinetics, after multiple and chronic dosing. Motor efficacy and dyskinesia were scored in MPTP-lesioned macaques (*Macaca fasicularis*; N=8) that had been previously exposed to levodopa and had developed responsive dyskinesias. Following 3 days of once-daily dosing of PF-9751, motor disability scores were significantly improved during the entire 6 hour scoring session vs. single vehicle dose. Similar to single dose levodopa, disability scores were reduced to near zero; however, motor improvement with PF-9751 was maintained for -the full 6 hour assessment period vs 2 - 3 hours for Levodopa. Dyskinesias were measured and were present, but to a lesser degree with PF-9751 compared to levodopa. We then examined the impact of PF-9751 when administered to macaques with MPTP-induced motor deficits and no prior exposure to levodopa. Motor disability and dyskinesia was measured after 30 consecutive days of once-daily administration of PF-9751. Motor disability was significantly reduced from vehicle condition. Contrary to what would be expected with levodopa dosing, no dyskinesias were observed after 30 consecutive days of PF-9751 administration. Taken together, these data show that tachyphlaxsis of motor response is not observed with the novel ligand class and highlight the potential for D1R agonist, PF-9751, to have continuous behavioral efficacy. This result also suggests that continuous activation of D1R by appropriate agonist does not carry increased risk of dyskinesia induction in non-primed animals, and may represent a mechanism for improving motor function without initiating or exacerbating dyskinesias in chronic disease conditions.

Disclosures: **D. Gray:** A. Employment/Salary (full or part-time):; Pfizer, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer, Inc. **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer, Inc. **W. Liu:** None. **K. Fonseca:** A. Employment/Salary (full or part-time):; Pfizer, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer, Inc. **E. Bezard:** A. Employment/Salary (full or part-time):; MOTAC, Inc.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.03/R3

Topic: C.03. Parkinson’s Disease

Title: Evaluation of the novel non-catecholamine D1 agonist, PF-142, against traditional D1 agonists in D1 receptor knockout and wild-type mice

Authors: *K. M. DLUGOLENSKI[1], R. GORCZYCA[2], D. GRAY[2], R. KOZAK[3]
[1]Psychiatry & Behavioral Disorders, Neurosci. Res. Unit, Pfizer Global Res., Cambridge, MA; [3]Neurosci. Res. Unit, [2]Pfizer, Cambridge, MA

Abstract: Dopamine is one of the most important neurotransmitters in the central nervous system (CNS). It is involved in almost every aspect including control of movement and cognition of brain functions. There is evidence for a shift in the status of dopamine transmission in multiple neuropsychiatric disorders linked mainly to D1 receptor signaling. The D1 receptor is the most widespread dopamine (DA) receptor and is expressed at higher levels than any other DA receptor (Dearry et al., 1990). D1 plays a critical role in orchestrating function within the prefrontal cortex (PFC) and striatum for neuro-adaptive processes. Traditional synthetic D1 agonists have been based on the catecholamine structure of dopamine and this has led to potent drug candidates. Unfortunately, the catecholamine structure may have also prohibited the therapeutic potential of those candidates. In this study we characterize the impact of a novel D1 agonist, PF-142, not based on the catecholamine structure of dopamine, using in vivo assays and compared it to traditional synthetic D1 agonists. PF-142, like the traditional partial and full D1 agonists, SKF-38393 and SKF-83959, respectively, increased locomotor activity in wild-type (WT) mice. Locomotor responses were effectively blocked by administration of a D1 antagonist. Similar to D1 agonists (Acquas, 1994), PF-142 increases acetylcholine (ACh) at the level of the PFC, as shown via microdialysis, in wild-type (WT) mice this effect is lost in the knockout (KO) mice. Interestingly, D1 KO mice showed a differential response to the D1 agonist classes in locomotor activity. In the D1 KO, PF-142 still had a locomotor response, albeit partially attenuated, while this effect is completely lost by SKF-38393 and SKF-83959. However, this partial response to PF-142 was still blocked by D1 antagonism. Moreover, repeated administration (5 day) revealed a very unusual response profile in that the PF-142 partial response seen in D1 KO mice on day 1 no longer occurs by day 3.

Disclosures: **K.M. Dlugolenski:** A. Employment/Salary (full or part-time):; Pfizer. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer. **R. Gorczyca:** A. Employment/Salary (full or part-time):; Pfizer. **D. Gray:** A. Employment/Salary (full or part-time):; Pfizer. **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.04/R4

Topic: C.03. Parkinson's Disease

Support: Industry Contract (Pfizer)

Title: Effects of a dopamine partial agonist on working memory in the aged rhesus monkey

Authors: *T. L. MOORE[1], R. L. SMITH[2], B. G. E. BOWLEY[2], R. J. KILLIANY[2], D. VOLFSON[3], D. L. GRAY[3], R. KOZAK[4]
[1]Boston Univ. Sch. Med., Boston, MA; [2]Anat. and Neurobio., Boston Univ. Sch. of Med., Boston, MA; [4]Neurosci. Res. Unit, [3]Pfizer, Cambridge, MA

Abstract: Background: Deficient D1 receptor signaling, particularly in the PFC, has been directly implicated in age-related declines in cognitive functions including memory capacity and flexibility in nonhuman primates (Goldman-Rakic and Brown, 1981) and humans (Ota et al., 2006). Working memory in both monkeys aged and monkeys experimentally depleted of DA was improved by the partial D1 receptor agonist (D1R), SKF38393 (Arnsten *et al.*, 1994). Accordingly, the PFC DA system is a strong target for therapeutic intervention to slow or reverse age related cognitive declines. In this study, we assess the effect of a novel class of non-catechol D1R agonists with favorable drug-like properties, PF-6294, on the performance of aged female rhesus monkeys in tasks of working memory and executive function. **Methods:** This study was divided into three drug/testing sessions. Eight monkeys received daily administration of one of three doses (0.0021, 0.021 and 0.24 mg/kg) or a placebo during each of the three sessions. A cross-over design was used and each monkey received two of the three doses and the placebo once during the study. Doses were randomly assigned to each monkey and treatments were administered daily over 3 weeks by subcutaneous injection one hour prior to the testing session which occurred 5 days/week. A six-week wash-out period occurred between each session during which no drug was administered and monkeys were not tested. During each session, we administered 2 tasks: Delayed Non-Matching to Sample (DNMS), with and without delays, and Delayed Recognition Span Task (DRST). **Results:** No significant effect of treatment was observed in the basic DNMS or delayed version of task. However, the mid-range dose significantly affected DRST performance. Specifically, monkeys administered the 0.021 mg/kg dose achieved a significantly greater span of correct responses than monkeys receiving placebo or other doses both acutely, day 1, and after repeated administration at day 4. **Conclusions:** These data demonstrate that this new class of non-catechol D1R agonists improves working memory span in aged monkeys. D1R-based pharmacotherapies represent an attractive target for the treatment of cognitive decline associated with age and warrant further investigation.

Disclosures: T.L. Moore: None. **R.L. Smith:** None. **B.G.E. Bowley:** None. **R.J. Killiany:** None. **D. Volfson:** None. **D.L. Gray:** None. **R. Kozak:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.05/R5

Topic: C.03. Parkinson’s Disease

Title: Impaired beta-arrestin recruitment and reduced desensitization by non-catechol agonism of the D1 dopamine receptor

Authors: *J. A. ALLEN[1,2], D. GRAY[2], S. MENTE[3], E. GUILMETTE[2], M. SALAFIA[4], R. E. O'CONNOR[4], D. VOLFSON[2], J. DAVOREN[3], R. KOZAK[2], M. D. EHLERS[2,5]
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Abstract: Introduction: Selective agonism of the dopamine D1 receptor (D1R) has been pursued for nearly 40 years as a therapeutic strategy for neurologic and psychiatric diseases due to the fundamental role of D1Rs in motor function, reward processing, and cognition. However, all known D1R-selective agonists are catechols, which are rapidly metabolized *in vivo*. Moreover, prolonged exposure to catechol agonists desensitizes the D1R, which reduces agonist response. As such, drug-like selective D1R agonists have remained elusive. Here we report a novel series of selective, potent non-catechol D1R agonists with excellent *in vivo* pharmacokinetics. These ligands stimulate adenylyl cyclase signaling, but exhibit distinct binding to the D1R orthosteric site that does not lead to desensitization or trigger recruitment of Beta-arrestin as observed with catechol ligands. **Methods:** A high throughput screen measuring D1R-mediated cAMP production was performed followed by chemical optimization of lead molecules. The novel ligands were characterized for their orthosteric binding mode and receptor selectivity using a combination of radioligand binding, homology modeling and receptor mutagenesis. Desensitization of Gs-mediated cAMP signaling was assessed using primary rat striatal neurons while beta-arrestin recruitment to D1Rs was examined by imaging arrestin2-GFP using TIRF microscopy. **Results:** Evaluation of nearly 3 million distinct compounds in a D1R functional screen yielded a single low affinity, non-catechol D1R agonist which was optimized through medicinal chemistry to create potent, highly selective, and orally bioavailable non-catechol agonists. Unlike catechol D1R agonists, non-catechol ligands did not trigger recruitment of beta-arrestin or receptor desensitization, despite strong activation of Gs/adenylyl cyclase. Structure-based modeling, receptor mutagenesis, and chemical biology probes further revealed that these unique agonist effects result from a novel binding interaction for non-catechols with key residues in extracellular loop 2. **Conclusions:** Taken together, these findings elucidate a unique orthosteric binding mode for selectively activating the D1 dopamine receptor, defines a molecular basis for ligand-specific recruitment of beta-arrestin and reveals structural

underpinnings for agonist functional selectivity at a GPCR. In addition, discovery of these highly selective D1R agonists with favorable drug-like properties with limited desensitization also provides therapeutic promise for treating neurologic and psychiatric diseases involving reduced dopaminergic signaling.

Disclosures: **J.A. Allen:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **D. Gray:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **S. Mente:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **E. Guilmette:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **M. Salafia:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **R.E. O'Connor:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **D. Volfson:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **J. Davoren:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **M.D. Ehlers:** A. Employment/Salary (full or part-time):; Pfizer, Inc.; Biogen Inc..

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.06/R6

Topic: C.03. Parkinson’s Disease

Title: Effects of a novel non-catechol D1 dopamine receptor class of agonists on working memory in rats

Authors: *D. YOUNG[1], D. MCGINNIS[2], D. S. CHAPIN[1], A. ROSSI[1], W. M. HOWE[3], D. VOLFSON[1], P. A. SEYMOUR[2], D. GRAY[1], R. KOZAK[1]
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Abstract: The neurotransmitter dopamine has long been known to play a critical role in a large swath of cognitive and behavioral domains. The D1 receptor (D1R), in particular, has been shown to be essential for motor control, reward sensitivity, cognitive function, and top-down executive control. Dysregulation of the dopamine system is believed to underpin several disabling neurologic and psychiatric disorders, including Parkinson’s, ADHD, addiction, and the cognitive impairments seen in schizophrenia. As such, selective activation of D1Rs has long been considered an attractive therapeutic strategy; however, all known D1R-selective agonists are catechols, which are rapidly metabolized, which has prevented D1R therapeutic development. We have recently discovered a novel series of non-catechol D1R agonist ligands with drug-like properties that could serve as a major advance toward investigating the therapeutic promise of the D1 agonist mechanism. This non-catechol class of ligands strongly activates Gs-adenylyl cyclase-cAMP signaling and, furthermore, does not trigger the recruitment of β-arrestin, a key mechanism leading to desensitization. Here, we investigate the behavioral

effects of these non-catechol D1R agonists on working memory in rats. Separate groups of animals were run on one of two assays, a radial arm maze (RAM) task or a touch-screen continuous trial-unique non-match-to-location (CTUNL) task. Animals in the RAM task were given a potent non-catechol D1R agonist (PF-6142; 0.01, 0.056, 0.178, 0.56, 1.78, 5.6 mg/kg), while CTUNL animals received either a high intrinsic activity (HIA; PF-9751; 0.056, 0.56, 1.78 mg/kg) or a low intrinsic activity (LIA; PF-9571; 0.032, 0.32, 1.0 mg/kg) non-catechol D1R partial agonist. In the RAM task, ketamine induced significant deficits that were alleviated in a clear inverted-U, dose-dependent manner by the D1R agonist. In the CTUNL task, both the HIA and LIA compounds improved working memory performance in response to a challenge, with the HIA producing the classic dopamine agonist bell-curve dose-response, while the LIA had a much more linear dose-dependent effect. Taken together, we show that non-catechol D1R agonists can provide beneficial behavioral effects in cognitive areas typically affected by a host of neuropsychiatric disorders. This, along with the favorable pharmacological profile of these compounds to not induce desensitization, may finally allow for the testing of several long-standing therapeutic hypotheses for activating D1R in neurologic and psychiatric illnesses, including Parkinson's disease and schizophrenia, as well as leading to novel therapeutic treatments for such disorders.

Disclosures: **D. Young:** A. Employment/Salary (full or part-time):; Pfizer Inc. **D. McGinnis:** A. Employment/Salary (full or part-time):; Pfizer Inc. **D.S. Chapin:** A. Employment/Salary (full or part-time):; Pfizer Inc. **A. Rossi:** A. Employment/Salary (full or part-time):; Pfizer Inc. **W.M. Howe:** A. Employment/Salary (full or part-time):; Pfizer Inc. **D. Volfson:** A. Employment/Salary (full or part-time):; Pfizer Inc. **P.A. Seymour:** A. Employment/Salary (full or part-time):; Pfizer Inc. **D. Gray:** A. Employment/Salary (full or part-time):; Pfizer Inc. **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer Inc.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.07/R7

Topic: C.03. Parkinson's Disease

Title: Novel non-catechol dopamine D1 receptor agonist pretreatment protects against the cognitive impairment induced by increased memory load in non-human primates

Authors: *G. V. WILLIAMS[1], R. KOZAK[2], A. ABBOTT[1], K. R. FONSECA[2], C. J. SCHMIDT[2], D. L. GRAY[2], S. CASTNER[1]
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Abstract: Working memory (WM) is a key determinant of long-term functional outcome in a number of psychiatric and neurological disorders. There is evidence from a number of different

approaches for a prefrontal cortex dopamine deficiency in both schizophrenia and normal aging that could be ameliorated by improving D1 receptor (D1R) signaling. We therefore tested the impact of PF-2562, a novel and highly selective partial D1R agonist with improved pharmacokenetic properties, on a WM challenge task, a manipulation that taps into the level of cognitive reserves, and is relevant to many neuropsychiatric and neurological conditions. Adult and aged-adult rhesus monkeys are trained to stability on the spatial delayed response task with mean correct performance ranging between 65 - 75% correct with an SEM $\leq$ 2.5%. Memory load was increased in increments for both the number of spatial locations to be remembered (+2 wells) and in the length of delays utilized in the task (N + 1 sec). Seven or more consecutive test sessions of stable responding where performance was within the animals' baseline range was required between memory load challenges. All animals were tested first on the high memory load challenge in order to establish baseline performance at this level. 3 doses of PF-2562 (0.0021, 0.022, and 0.24 mg/kg SC) and vehicle were tested in random order. Both the aged-adult and adult groups showed a significant reduction in scores on the high memory load challenge. Both groups also benefited from PF-2562 administration. However, for the adult animals, only the mid dose (0.022 mg/kg) improved performance, indicating a sharp, inverted-U response. In contrast, aged-adult animals showed a strong response at the highest dose (0.24 mg/kg), indicating a more monotonic dose-response. These findings suggest that this new class of non-catechol D1R agonist prevents working memory impairment under challenging conditions; however, the profile of this effect is age-dependent. These results suggest that novel D1R agonists could be used to treat the cognitive decline associated with neurological disorders and warrant further investigation.

Disclosures: G.V. Williams: 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.; Pfizer Inc. **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer Inc. **A. Abbott:** 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.; Pfizer Inc. **K.R. Fonseca:** A. Employment/Salary (full or part-time):; Pfizer Inc. **C.J. Schmidt:** A. Employment/Salary (full or part-time):; Pfizer Inc. **D.L. Gray:** A. Employment/Salary (full or part-time):; Pfizer Inc. **S. Castner:** 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.; Pfizer Inc..

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.08/R8

Topic: C.03. Parkinson's Disease

Title: Effects of pretreatment with novel non-catechol full D1 agonist on working memory in the nonhuman primate acute ketamine model

Authors: *R. KOZAK[1], G. V. WILLIAMS[2], P. A. SEYMOUR[1], K. FONSECA[1], P. TRAPA[1], W. LIU[1], C. J. SCHMIDT[1], A. L. ABBOTT[2], D. L. GRAY[1], S. CASTNER[2]
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Abstract: Working memory (WM) is significantly impaired and a key indicator of functional outcome in multiple neuropsychiatric disorders. In both schizophrenia and aging, a PFC hypodopaminergic state has been hypothesized to occur, which might benefit from treatment with D1R agonists. In the present study, we investigated the ability of a novel, and highly selective, non-catechol class of D1R agonists with superior pharmacodynamic properties to reverse ketamine-induced WM impairment. For this aim, we tested both a full agonist, PF-3628, and a partial agonist, PF-2562. Nine or 10 monkeys (9 rhesus and 1 stumptail) were randomly assigned to receive either vehicle, PF-3628 (0.00025, 0.0025 and 0.06 mg/kg; S.C.), or PF-2652 (0.003, 0.015, and 0.06 mg/kg. P.O.) at 1h prior to testing on the spatial delayed response task and 45 minutes prior to IM administration of ketamine (median 1.0 mg/kg) or vehicle. Behavioral observations of the home cage were measured 5-10 minutes prior to testing. Pretreatment with PF-3628 prior to an acute ketamine challenge prevented ketamine's induced impairment in spatial WM only at the middle dose of 0.0025 mg/kg. Both lower dose and higher dose of the compound were found to be ineffective, revealing the expected behavioral inverted-U for the ability of this compound to enhance cognition. The cognitive improvement at 0.0025 mg/kg corresponded to a reduction in the mean number of errors at both long and short delays. However, PF-2652 yielded significant cognitive enhancement of spatial WM at both the low and high doses and reduced errors at both long and short delays. Further, unlike PF-3628 that was without influence on ketamine-induced positive-like behavioral symptoms, PF-2562 showed a trend towards reducing this effect, but did not alter normal psychomotor activity. Overall, the data show that, similar to standard catechol D1 agonists, these novel compounds significantly reversed the ketamine-induced deficit in WM, and that this positive effect occurred at a low receptor occupancy (<5%) and showed, as expected, an inverted-U shape. However, the lower intrinsic activity compound has a broader dose range for efficacy than the full D1 agonist. These findings indicate that this novel class of D1 agonists is efficacious in a key cognitive domain that is impacted under conditions in which NMDAR transmission is impaired, as hypothesized in schizophrenia, and highlight its therapeutic potential.

Disclosures: **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer Inc. **G.V. Williams:** 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.; Pfizer Inc.. **P.A. Seymour:** None. **K. Fonseca:** A. Employment/Salary (full or part-time):; Pfizer Inc. **P. Trapa:** A. Employment/Salary (full or part-time):; Pfizer Inc.. **W. Liu:** None. **C.J. Schmidt:** A. Employment/Salary (full or part-time):; Pfizer Inc. **A.L. Abbott:** 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.; Pfizer.com. **D.L. Gray:** A. Employment/Salary (full or part-time):; Pfizer Inc. **S. Castner:** 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.; Pfizer Inc..

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.09/R9

Topic: C.03. Parkinson’s Disease

Title: D1-selective partial agonist PF-9571 alters qEEG signals in a dose-dependent manner

Authors: *D. L. BUHL[1], G. J. DEMARCO[2], T. KISS[1], D. VOLFSON[1], K. R. FONSECA[1], P. TRAPA[1], D. L. GRAY[1], R. KOZAK[1]
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Abstract: Dopamine 1 receptors (D1Rs) are highly expressed in the prefrontal cortex and striatum of the brain and play a central role in synaptic plasticity as well as basal ganglia-mediated function. Agonists acting at the D1R have been shown to increase wakefulness and alter electroencephalography (EEG) power in rodents (Kropf & Kushinsky, 1993). In the present study, we assess a novel class of selective D1R non-catechol partial agonist, PF-9751, on neural activity using quantitative electroencephalography (qEEG) in Cynomolgus macaques (*Macaca fasicularis*; N=4). Following overnight baseline recordings from Cz (central), P4 (parietal), and F4 (frontal; all referenced from occipital Oz), animals were treated with vehicle, 0.05 (47% receptor occupancy [RO]/20% intrinsic activity [IA]), 0.1 (63% RO/28% IA), or 0.2 (78% RO/34% IA) mg/kg of PF-9571 via oral gavage using a randomized, cross-over design. qEEG signals were recorded 24 hours prior to and 24 hours following dosing. Using these signals, we developed and hand-validated a semi-automated sleep scoring algorithm to evaluate sleep architecture. We observed a dose-dependent decrease in low delta-band (0.5-2.5 Hz) power and a transient, dose-dependent increase in power in the higher frequencies, including beta (16-24 Hz) and gamma (24-50 Hz), were observed. No significant effects on EEG power were noted at the lowest dose. Although a dose-dependent trend in delaying sleep onset was observed, no significant changes in PSG were noted. The clear and dose-dependent changes in qEEG signals suggest that D1 partial agonist PF-9571 shows the expected neuronal activities associated with D1 receptor activation and highlight its potential to address significant unmet medical needs.

Disclosures: **D.L. Buhl:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **G.J. DeMarco:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **T. Kiss:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **D. Volfson:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **K.R. Fonseca:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **P. Trapa:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **D.L. Gray:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer, Inc..

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.10/R10

Topic: C.03. Parkinson's Disease

Title: Novel non-catechol D1 receptor agonist exhibits sustained *In vivo* pharmacological activity

Authors: *P. L. TIERNEY[1], S. M. LOTARSKI[1], A. M. ROSSI[1], D. VOLFSON[1], K. FONSECA[1], P. TRAPA[1], G. J. DEMARCO[2], X. CHEN[1], D. GRAY[1], R. KOZAK[1]
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Abstract: Dysfunctional dopamine signaling is a core component of the pathophysiology of Parkinson's disease. Current D1 receptor (D1R) compounds have limited therapeutic potential due to their poor CNS penetration, negligible oral bioavailability, rapid metabolism and propensity to cause receptor desensitization. We have developed a novel non-catechol class of D1R agonists with a pharmacodynamics profile exhibiting reduced tachyphylaxis in both a monkey eye-blink paradigm and rodent model of Parkinson's disease. In both behavioral assays, doses and frequency of dosing for comparison of drug effects were selected to achieve similar D1R receptor occupancy. All animal procedures were conducted with approval of the Pfizer Institutional Animal Care and Use Committee. Eye blink rates (EBR) can be used as an indirect predictor of activity at CNS dopamine receptors. We therefore measured the effect of PF-2334 (0.6 mg/kg BID, P.O), a non-catechol D1R agonist, on EBR and compared it to the effect of the catechol agonist A-77636 (0.1 mg/kg, S.C.) in male cynomolgus macaques (n = 3). A single dose of A-77636 induced a 2-3 fold increase in EBR compared to baseline and this increase was sustained over several hours. However, the A-77636-evoked EBR increase was progressively and significantly attenuated with subsequent doses. In contrast, the PF-2334 increase in EBR was sustained after multiple days of dosing, with no statistical difference between doses. The effect of PF-2334 was then tested in the 6-OHDA animal model of Parkinson's disease. Sprague-Dawley rats with unilateral 6-OHDA lesions (n=17) were individually monitored for rotational behavior and dosed using a crossover design (2-week washout period). In each treatment period

animals received six doses of either A-77636 (0.32 mg/kg S.C.) or PF-2334 (10.78 mg/kg, P.O.) administered every 12 h followed by a single dose of the D2 agonist quinpirole (0.1 mg/kg S.C.). After 72 hours of chronic treatment with A-77636, rats displayed near-zero contralateral rotational behavior. In contrast, PF-2334 treated animals were still rotating at the 72-hour time point. The absence of rotational behavior under A-77636 was likely due to D1R tachyphylaxis since treatment with the D2 agonist was able to restore rotational behavior. The persistent in vivo pharmacodynamic response of PF-2334 confirms our previous in vitro findings and demonstrates a limited receptor desensitization liability for this non-catechol D1R agonist. Therapeutically durable D1R agonism by PF-2334 can be a critical new treatment option for not just Parkinson's disease but other neurodegenerative disorders where deficits in dopamine signaling are present.

Disclosures: **P.L. Tierney:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **S.M. Lotarski:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **A.M. Rossi:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **D. Volfson:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **K. Fonseca:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **P. Trapa:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **G.J. DeMarco:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **X. Chen:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **D. Gray:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **R. Kozak:** A. Employment/Salary (full or part-time):; Pfizer, Inc..

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.11/S1

Topic: C.03. Parkinson's Disease

Title: Impact of the aplha4Beta2 partial agonist Varenicline on gait and motor coordination alterations in a rat model of Parkinson's disease

Authors: *A. M. ROSSI[1], M. MARSHALL[2], W. M. HOWE[4], R. KOZAK[3]
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Abstract: Disruptions in limb coordination, gait, and increased fall propensity are hallmarks of neurodegenerative disorders such as Parkinson's disease that are not ameliorated by standard dopamine replacement therapies. Alterations of gait and fall propensity are hypothesized to arise as top-down, cognitive control of motor output declines as a result of dual dysfunction of striatal dopaminergic and forebrain cholinergic systems. α4β2 nAChR selective nicotinic receptor (nAChR) agonists increase cholinergic modulation of top down control. Therefore α4β2 nAChR agonists may represent a promising option for correcting gait disruptions. One such α4β2 nAChR agonist is the smoking cessation aid Varencline, which has been shown to improve performance

in cognitive tasks dependent on top-down circuitry and cortical cholinergic signaling. In the present set of experiments, we sought to test the capacity of Varenicline to ameliorate gait disruptions associated with striatal dopaminergic depletion in rats. As a first step, two cohorts of animals (sham lesion and unilateral 6-OHDA striatal lesion) were trained to run on a treadmill. Parametric variations of treadmill speed and angle were employed to provide a dynamic estimate of limb coordination and potentiate the delineation of specific alterations following loss of dopaminergic innervation of the striatum. Results, so far, indicate that there are no gross group differences in the capacity of animals to learn to run on the treadmill or achieve sustained bouts (>6 s) of running at different velocities and angles. Regarding gait symmetry and forepaw/hind paw coordination during running, dopaminergic depletion was associated with alterations in stride length, duration, paw angle, and unilateral inter-leg coordination. On-going experiments directly compare the capacity of Varenicline to normalize these alterations in lesioned animals relative to l-dopa. The combined results of the present studies extend our knowledge of the neural mechanisms contributing to the alterations in gait that accompany neurodegenerative diseases like Parkinson's, and illustrate the potential benefit of novel, non-dopaminergic treatment strategies such as α4β2 nAChR agonists.

Disclosures: **A.M. Rossi:** A. Employment/Salary (full or part-time):; Pfizer Inc. **M. marshall:** None. **W.M. Howe:** None. **R. Kozak:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.12/S2

Topic: C.03. Parkinson's Disease

Support: Grants-in-Aid for Scientific Research (B) No. 24390298 from Japan Society for the Promotion of Science

Title: Relation of motor and non-motor symptoms with density of metabotropic glutamate receptors subtype 1 measured with ^{11}C-ITMM PET in de novo Parkinson's disease

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Abstract: Introduction Glutamate receptors are divided into 2 types based on their biological functions and molecular structures: ionotropic and metabotropic types. Metabotropic glutamate receptor subtype 1 (mGluR1) is one of the group 1 receptors. However, the relationship between the mGluR1 and Parkinson's disease (PD) remains to be determined. The purpose of this study was to investigate the mapping of the mGluR1 in elderly healthy controls and de novo patients with PD using *N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-4-^{11}C methoxy-*N*-methylbenzamide (^{11}C-ITMM) and positron emission tomography (PET), and to assess whether the mGluR1 is involved in the damaged dopaminergic system in PD. We also determined the correlations of motor and non-motor symptoms with the brain densities of mGluR1. Methods We studied 25 normal subjects and nine de novo patients with PD. Informed consent was obtained from all subjects. We used to evaluate severity of non-motor and motor symptoms with The Movement Disorder Society-sponsored revision of the Unified PD Rating Scale (MDS-UPDRS) part I and III, respectively. The patients were divided into two groups for non-motor and motor symptoms, using MDS-UPDRS part I and III. A dynamic series of decay-corrected PET scans was performed for 90 minutes starting at the time of the injection of 700 MBq of ^{11}C-ITMM. Circular ROI of 10-mm in diameter were placed on the PET images. We calculated regional time activity curves in the tissue (tTACs) from the dynamic data and ROIs, and we evaluated binding of ^{11}C-ITMM to mGluR1s in the regions as a distribution volume ratio (*DVR*) using tTACs, a graphical analysis with the occipital lobe as the reference region. Unpaired *t*-tests were used to compare the *DVR*s from ^{11}C-ITMM between the healthy and patient groups, and the *DVR*s between the severe and mild groups for motor and non-motor symptoms. The level of significance was set at $p<0.05$. Results The *DVR* of the patients was significantly lower than the controls in the cerebellar hemisphere, and temporal and parietal lobe. Within the patient group, The *DVR* showed no significant relationship with severity for both motor and non-motor symptom in all regions. Conclusion The cerebellar circuit does not directly interact with the basal ganglia. In Parkinson's disease, the inhibitory output from the basal ganglia to the thalamus is elevated, and the excitatory output from the thalamus to the cerebral cortex is attenuated. Our results may be involved in the decrease in dopamine and parkinsonism such as akinesia, although our data did not show involvements in severity of parkinsonism.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.13/S3

Topic: C.03. Parkinson's Disease

Support: NIH Grant F32 DC014399

NIH Grant RO1 DC014358

Title: Gad1 is dysregulated in the substantia nigra and locus coeruleus in early-stage PD

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Abstract: Early-stage Parkinson disease (PD) is hypothesized to manifest in brainstem regions, including the locus coeruleus, and non-dopaminergic neuromodulatory systems, such as GABA, are often dysregulated. At 8 months, the *Pink1* -/- rat model of PD exhibits detectable fine motor and cranial sensorimotor deficits as well as non-dopaminergic pathology including reduced norepinephrine concentrations and aggregated alpha-synuclein in the locus coeruleus. In this study, we hypothesized that *Pink1* -/- rats would demonstrate differential expression of GABA compared to age-matched wildtype (WT) controls. To test this hypothesis, real time qPCR was used to determine relative expression levels of *Gad1* (glutamate decarboxylase 1) in micropunched tissue samples (striatum, substantia nigra, locus coeruleus). The data show that in *Pink1* -/- rats (n=12) *Gad1* is significantly downregulated in the substantia nigra (p=0.04) and upregulated in the locus coeruleus (p=0.06) compared to WT (n=6). There was no difference in *Gad1* expression in the striatum (p>0.05). Together, these data support the working hypothesis that a decrease in GABA in the substantia nigra may act to increase dopaminergic activity by reducing neurotransmitter inhibition. An increase of GABA in the locus coeruleus could account for an increase in noradrenergic inhibition; this should be studied directly in the future. Data from this study suggest that *Pink1* -/- early-onset behavioral pathology may be related to effects of *Gad1* dysregulation, and not uniquely dopamine loss. Likewise, disruptions to GABAergic functions represent a unique complexity in the *Pink1* -/- animal model that parallels early-stage PD pathology observed in humans.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.14/S4

Topic: C.03. Parkinson’s Disease

Title: Single nucleotide polymorphisms in tyrosine hydroxylase and dopamine beta hydroxylase: Association with altered non-motor symptoms in parkinson’s disease

Authors: *E. GONZALEZ-LOPEZ[1], I. TEKIN[2], M. M. LEWIS[3], X. HUANG[4], K. E. VRANA[5]
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Abstract: The role of genetics in the pathogenesis and progression of Parkinson's disease (PD) remains an important area of investigation. Recent reports from our laboratory found that a single-nucleotide polymorphism in tyrosine hydroxylase (TH), Val81Met (rs6356), was associated with higher freezing of gait (FOG) scores in PD individuals that are homozygous for the variant. FOG arises in most PD patients in the later stages of the disease, and both norepinephrine (NE) and dopamine signaling dysfunctions are proposed to contribute to FOG. Whereas the dopaminergic system is central to the movement dysfunction in PD, impairment of the noradrenergic system contributes to the non-motor aspects of the disease such as depression, anxiety, sleep disturbances, and olfactory deficits. Modulation of the noradrenergic system has been shown to ameliorate both motor and non-motor PD symptoms and it is proposed to be neuroprotective. Noradrenergic neuron loss in the locus coeruleus has been shown to precede the loss of dopaminergic neurons in the substantia nigra of PD patients. Dopamine-β-Hydroxylase (DβH) is present in the synaptic vesicles of locus coeruleus noradrenergic neurons and converts DA to NE. In this study, we assessed a cohort of patients diagnosed with PD (n=106) and aged matched controls (n=78) for the genetic variant of DβH, Arg549Cys (rs6271). This polymorphism is located in a highly conserved tetramerization domain that is thought to be important for the maintenance of proper DβH function. We found that the Arg549Cys substitution is over-represented in primarily Caucasian PD patients compared to controls. The frequency of the DβH Arg549Cys allele was increased significantly in the PD group compared to controls, with an odds ratio for a DβH Arg549Cys allele being 3.9 times higher than the wild-type allele (p=0.0056). This polymorphism was correlated with non-motor symptoms, whereas a previously described TH polymorphism, Val81Met was associated with both motor and non-motor symptoms. The results suggest that these polymorphisms may contribute to the prevalence and severity of select motor and non-motor symptoms in PD.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

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Topic: C.03. Parkinson’s Disease

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Army Research Office W911NF-16-1-0474

Title: Electrochemical recording of pharmacologically modulated dopamine from sensors chronically implanted in striatum of awake non-human primates

Authors: *H. N. SCHWERDT[1], H. SHIMAZU[1], K. AMEMORI[1], S. AMEMORI[1], S. HONG[1], T. YOSHIDA[1], R. LANGER[2], M. J. CIMA[2], A. M. GRAYBIEL[1]
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Abstract: Dopamine neurotransmission is an important signaling mechanism of the brain that modulates many essential behaviors that are degraded in a range of neurologic and neuropsychiatric disorders. The ability to record these neurotransmitters over long time-periods is necessary for accurate diagnosis of pathologic states and for improvement of treatment in the future. However, no one has yet established these techniques for chronic recording in non-human primates, which is necessary for translation to the human. We implanted multiple carbon fiber microelectrode (CFM) sensors into the striatum of macaque monkeys. Using well-established fast-scan cyclic voltammetry (FSCV) methods, we recorded sub-second changes in dopamine concentration from the implants over months. Putative dopamine-generated currents were identified by correlation to *in vitro* standards ($R > 0.8$) and regression analysis to exclude signals containing residuals above a calculated tolerance threshold ($Q_\alpha = 46$). Based on these criteria, we evaluated the frequency of measured dopamine release before and after pharmacologic treatment. We administered raclopride (0.05-0.15 mg/kg, i.m.), a D2 receptor antagonist, to modulate endogenous dopamine release. The frequency of measurable dopamine increased following raclopride treatment. The increased dopamine signaling was observed across multiple sessions and implanted sensors. Through the use of a modular chamber platform, we could introduce new CFM sensors in the same animal. This allowed us to compare and cross-validate measurements of these modulatory effects from both the chronic and acute CFM sensors. . These types of measurements could be useful in clinical applications, for example, to monitor the effects of L-DOPA or other treatments on neurotransmitter signaling, as used in treating Parkinson's disease and other disorders. With acutely implanted sensors, we also measured dopamine release as evoked by reward and by electrical stimulation of dopamine-containing neurons and/or fibers. These results demonstrate the potential for recording relevant changes in dopamine concentration in the striatum over prolonged periods, which is important for clinical translation.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

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Program#/Poster#: 047.16/T2

Topic: C.03. Parkinson’s Disease

Title: The D1PAM DETQ reverses hypo-locomotion induced by reserpine in hD1KI mice a preclinical model for motor symptoms in Parkinson's Disease

Authors: *J. FALCONE, L. THOMPSON, B. L. ADAMS, J. HAO, K. KNOPP, D. L. MCKINZIE, R. F. BRUNS, K. A. SVENSSON
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Abstract: Reduced brain levels of dopamine associated with Parkinson’s disease (PD) lead to impaired motor function including muscle rigidity, bradykinesia, or akinesia. We utilized a behavioral locomotor activity (LMA) model that tested the ability of DETQ, a novel D1 positive allosteric modulator (D1PAM), to reverse the motor impairment induced by treatment with the dopamine depleting agent reserpine. These studies were performed using transgenic humanized dopamine D1 knock-in mice (hD1KI) in which both copies of the murine D1 receptor were replaced with its human counterpart. It has been established both neurochemically and behaviorally that depletion of the neurotransmitter dopamine is responsible for the motor dysfunction seen in reserpine-treated animals. Neurochemical analysis of neurotransmitter and metabolite levels from hD1KI mice treated with reserpine were performed on post mortem brain striatal tissues to establish that dopamine levels had been depleted. In these studies, a low dose of reserpine (0.3 mg/kg, 18h) resulted in partial (~50%) striatal dopamine depletion associated with hypo-locomotion. The D1PAM DETQ (3-30 mg/kg, PO) completely reversed this hypo-locomotion. There was a profound effect of low dose reserpine on gait performance using video tracking monitoring. Studies are in progress assessing the effects of D1PAM on gait using this model. A high dose of reserpine (2.5 mg/kg, 18h) resulted in complete (>95%) dopamine depletion and strong motor inhibition (akinesia). In this case, DETQ (10 and 30 mg/kg, PO) dosed alone, failed to significantly reverse the akinesia. However, when combined with threshold doses of L-DOPA/Carbidopa (100-400/100 mg/kg) DETQ acted in a synergistic manner to reverse the akinesia induced by a high dose of reserpine. Studies in progress also address the interactions between DETQ and the selective D1 agonist SKF82958 in these models.
These data indicate that a D1PAMs like DETQ have therapeutic potential as monotherapy in early stages of PD or as combination therapy with L-DOPA.

Disclosures: J. Falcone: None. **L. Thompson:** None. **B.L. Adams:** None. **J. Hao:** None. **K. Knopp:** None. **D.L. McKinzie:** None. **R.F. Bruns:** None. **K.A. Svensson:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.17/T3

Topic: C.03. Parkinson's Disease

Support: NIH R01NS097783

NIH K23NS080988

American Heart Association 14GRNT20150004

National Center for Advancing Translational Science CTSA award No. UL1TR000445

Title: Striatal and extrastriatal D_2-like receptor expression in Parkinson's disease patients with compulsive reward-driven behaviors

Authors: *A. STARK[1], K. PETERSEN[1], P. TRUJILLO[1], R. KESSLER[2], D. H. ZALD[3], D. CLAASSEN[1]
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Abstract: The nigrostriatal and mesocorticolimbic dopamine networks regulate reward-driven behavior. Regional alterations to mesolimbic dopamine $D_{2/3}$ receptor expression are evident in disorders such as drug seeking and addiction. Parkinson's disease (PD) patients are frequently prescribed D_2-like dopamine agonist (DAgonist) therapy for motor symptoms, yet a proportion develop clinically significant behavioral changes known as impulsive and compulsive behaviors (ICBs). Here, we assessed $D_{2/3}$ receptor binding distinctions in PD patients with and without ICB. We identified 17 PD patients with active ICB symptoms, and 18 without, where groups were matched for age, disease duration, disease severity, and dopamine therapy dose. In the off medication state, all completed PET imaging procedures with [^{18}F]fallypride, a high affinity D_2-like receptor ligand. Data were analyzed using the simplified reference tissue method, with putamen and cerebellum serving as the receptor-rich and reference regions, respectively. Mean regional binding potential (BPnd) was examined using manually segmented regions-of-interest (ROIs) via a general linear model (GLM) covarying for age and United Parkinson's Disease Rating Scale Part II score with FDR controlled at 0.1 to correct for multiple comparisons. Striatal differences between ICB+/ICB- patients localized to the ventral striatum ($p=0.016$) and putamen ($p=0.029$), where ICB+ subjects had reduced non-displaced binding potential. In PD-ICB patients, self-reported severity of symptoms positively correlated with midbrain $D_{2/3}$ receptor binding potential ($p=0.011$). Group differences in regional $D_{2/3}$ binding potential relationships

were also notable: ICB+ (but not ICB-) patients expressed positive correlations between BPnd in the midbrain and caudate, putamen, globus pallidus, and amygdala, as tested by a GLM with FDR controlled at 0.1. These findings support the hypothesis that compulsive behaviors seen in PD are associated with relatively reduced striatal $D_{2/3}$ expression, similar to changes in comparable behavioral disorders. They also suggest that ventral midbrain dopaminergic projections throughout nigrostriatal and mesolimbic networks are unique in ICB+ patients, and may account for differential DAgonist therapeutic response.

Disclosures: A. Stark: None. **K. Petersen:** None. **P. Trujillo:** None. **R. Kessler:** None. **D.H. Zald:** None. **D. Claassen:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

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Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS070825

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University of Pittsburgh

Title: The effects of N-acetylcysteine on survival of MN9D cells in an *In vitro* model of Parkinson's disease

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Abstract: Oxidative stress is implicated in multiple neurodegenerative diseases. One such disease is Parkinson’s disease (PD), which is characterized in part by motor deficits that are due to loss of the dopamine (DA) producing cells of the substantia nigra. MN9D cells are a dopaminergic-like cell line that has many of the properties of DA neurons, including high levels of the DA synthesizing enzyme, tyrosine hydroxylase; the ability to synthesize DA; and a functioning DA transporter (DAT). N-acetylcysteine (NAC) is an anti-oxidant. It is also a precursor for glutathione, a more potent anti-oxidant. We used two toxins to induce the death of MN9D cells. To expose the cells to external reactive oxidative species (ROS), we used hydrogen peroxide (H_2O_2). To examine the impact of ROS generated from within the cells we used 6-hydroxydopamine (6-OHDA), a compound that under certain conditions is taken up into the cells through DAT prior to forming ROS intracellularly. In addition, we examined two paradigms for

the addition of NAC: a “protective” paradigm in which NAC was present 1 hr prior to addition of either H_2O_2 or 6-OHDA, and a “rescue” paradigm in which NAC was added only after removal of the toxin. NAC added prior to a toxin had a robust protective effect in a dose-dependent manner on toxicity induced by either H_2O_2 or 6-OHDA up to a 10 nM dose of NAC as measured by the ATP assay, Cell Titer Glo. NAC also rescued the cells when added after the removal of 6-OHDA, increasing the ATP reading by approximately 40% above the 6-OHDA alone control. We are continuing to investigate the time course for the restorative paradigm to determine how long after a toxin exposure NAC can be added and still be effective in combating the effect of H_2O_2 or 6-OHDA. We will also examine whether NAC is working alone as an antioxidant or via an increase intracellular glutathione.

Disclosures: **M.J. Zigmond:** None. **K.A. Meehan:** None. **J.D. Jaumotte:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.19/T5

Topic: C.03. Parkinson’s Disease

Support: DGAPA IT-202417

Title: The effect of enriched environment on motor function in unilateral lesioned rats implanted with dopamine matrix

Authors: *M. PIZARRO-RODAS[1], P. VERGARA-ARAGON[1], G. VALVERDE-AGUILAR[2], N. H. MONTES-CRUZ[1], B. I. K. MEZA-AUPART[1], L. E. DOMINGUEZ-MARRUFO[1]
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Abstract: The Enriched Environment (EE), induces plasticity responses in the adult brain; these can be observed as simple as biochemical parameters, gliogenesis, neurogenesis, improvement on the learning and promotes the survival of implants on the dopaminergic pathway. The EE is a behavioral condition that provides the subject with additional stimulus than those that it receives on the everyday life. The EE for animals consists on placing them in big boxes with toys, like a spinning wheel; which are placed on different locations from the box everyday. The purpose of this project was to analyze the effects of an EE on the motor alterations observed on rats with induced hemiparkinsonism and to which a TiO2/DA matrix had been implanted in the caudate nucleus. 36 male Wistar rats were used (250-270g) divided on 6 groups; Group 1) Control (intact rats); Group 2) Control with EE; Group 3) Unilateral lesion (6OHDA) in the nigrostratial way; Group 4) Unilateral lesion with EE; Group 5) Unilateral lesion and TiO2-DA matrix implant in the caudate nucleus, and Group 6) Unilateral lesion and TiO2-DA matrix implant with EE. The

EE groups were assigned everyday on an EE, while the groups with no EE were simply allocated in normal environments. On the training period (three weeks), the animals were allocated in both environments before the lesions were made. The behavior tests were realized every 7 days; all the while the EE sessions continued up to four weeks after the lesion. The qualitative analysis of the movements during the motor tests and the rotation induced with drugs showed no statistical significant difference between the control EE group and the TiO2-DA with EE group. Probably the continuous dopamine liberation with the EE effects are the cause of the anxiety diminution measured with behavioral parameters, as well they might be responsible for the histological changes observed in the groups treated with EE.

Disclosures: M. Pizarro-Rodas: None. **P. Vergara-Aragon:** None. **G. Valverde-Aguilar:** None. **N.H. Montes-Cruz:** None. **B.I.K. Meza-Aupart:** None. **L.E. Dominguez-Marrufo:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

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Program#/Poster#: 047.20/T6

Topic: C.03. Parkinson’s Disease

Support: Spanish Ministerio de Economia y Competitividad (SAF2016-48532-R)

ISCIII, CIBERNED (CB06/05/0055)

Title: Altered striatal amino acid levels in parkinsonian and dyskinetic mouse models

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Abstract: Perturbations in the cerebral levels of various amino acids are associated with neurological disorders, and previous studies have suggested that such alterations have a role in the motor and non-motor symptoms of Parkinson disease. However, the different contributions of parkinsonism and L-DOPA-induced dyskinesia on amino acids changes remain largely unknown. In this study, we used intact and 6-OHDA-lesioned C57Bl6 mice. The lesioned mice were chronically treated with daily doses of saline (parkinsonian) or L-DOPA for two weeks (dyskinetic). Free amino acids (glutamate, glutamine, aspartate, GABA, glycine, taurine, tyrosine, lysine and alanine) tissue levels were examined in the dorsal striatum using high-pressure liquid chromatography. We found that glutamate striatal levels were unaffected in parkinsonian and dyskinetic mice compared to intact animals. However, glutamine increases

after 6-OHDA and returns to normal levels with L-DOPA treatment, suggesting increased striatal glutamatergic transmission with lack of dopamine. In addition, glycine and taurine levels are increased following dopamine denervation and restored to normal levels by L-DOPA. Interestingly, dyskinetic animals showed increased levels of GABA and tyrosine, while aspartate striatal tissue levels are not altered. Our results suggest, that chronic L-DOPA treatment, besides normalizing the altered levels of some amino acids after 6-OHDA, robustly increases striatal GABA and tyrosine levels which may in turn contribute to the development of L-DOPA-induced dyskinesia.

Disclosures: O. Solís Castrejón: None. **A.S. Herranz:** None. **P. García-Sanz:** None. **R. Moratalla:** None.

Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.21/T7

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01 AG52606; William & Ella Owens Medical Research Foundation

Title: Neurite arborization deficits in dopamine neurons in the MitoPark mouse model of Parkinson’s Disease

Authors: *W. B. LYNCH[1], A. L. SHARPE[1,3], S. Y. BRANCH[1], S. DOMINGUEZ-LOPEZ[1], S. LI[2], M. J. BECKSTEAD[1]
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Abstract: Parkinson’s disease (PD) is characterized by the progressive loss of dopamine (DA) neurons in the substantia nigra, which in turn leads to severe motor impairments. While it is thought that DA neuronal impairment begins to develop years before observable motor deficits, the specific morphological and functional changes that contribute to declining DA neuronal function are unknown. To address this gap in knowledge we are studying DA neuronal decline in MitoPark mice. MitoPark mice lack the gene coding for mitochondrial transcription factor A specifically in DA neurons, which across age produces a progressive decline of neuronal function and related behavior. Our previous work identified an increased membrane resistance and a decreased cell capacitance in DA neurons, possibly suggesting deficits in neurite branching in MitoPark mice. The results from the present study show an initial neurite reduction in DA neurons of MitoPark mice starting at 15-20 weeks of age, an age that precedes wholesale neuronal death. MitoPark mice at older ages exhibited a further neurite reduction, illustrating a progressive age-related decline of DA neurite branching in the substantia nigra. We also

observed declining motor abilities in 17-20 week old mice of both sexes as evidenced by impairments in both rotarod and open field tests. Our results provide quantitative evidence of morphological deterioration in individual DA neurons in a progressive mouse model of PD. Further, this work possibly suggests that treatments targeting the preservation of neurite arborization in humans with PD could extend the time before the onset of declining DA neurotransmission and debilitating motor symptomatology.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

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Topic: C.03. Parkinson’s Disease

Support: NIH R01NS097783

NIH K23NS080988

American Heart Association 14GRNT20150004

National Center for Advancing Translational Science CTSA award No. UL1TR000445

Title: Mesolimbic D_2-like receptor expression in patients with Parkinson's disease

Authors: *P. TRUJILLO[1], A. J. STARK[1], K. PETERSEN[1], R. KESSLER[2], D. H. ZALD[3], D. O. CLAASSEN[1]
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Abstract: Parkinson’s disease (PD) is a neurodegenerative condition characterized by nigrostriatal dopamine loss with dopamine responsive motor symptoms. Additional symptoms include nonmotor neuropsychiatric comorbidities, ranging from depression and apathy, to hallucinations and delusions, emphasizing the importance of the extrastriatal pathophysiologic process in PD. $D_{2/3}$ expressing cell populations in mesolimbic brain regions appear greatest in the amygdala, hippocampus, and thalamus, where previous studies employing positron emission tomography (PET) describe $D_{2/3}$ expression changes in PD populations in both striatal and extrastriatal regions. No investigations have probed the full extent of dopaminergic limbic networks due to inherent radioligand limitations. Here, we examined 35 PD patients and 31 age-matched healthy controls (HC) to test the hypothesis that PD is associated with divergent

mesolimbic patterns of $D_{2/3}$ expression. PD patients completed PET imaging procedures in the off-dopamine state (having withheld both dopamine agonists and levodopa) using [^{18}F]fallypride, a high affinity $D_{2/3}$ receptor ligand with the ability to accurately quantify binding potential (BPnd) in both striatal and extrastriatal areas. Data were analyzed using the simplified reference tissue method, with putamen and cerebellum serving as the receptor-rich and reference regions, respectively. Mean regional BPnd was examined using manually segmented regions-of-interest (ROIs) via a general linear model covarying for age and ROI volume, with false discovery rate (FDR) controlled at 0.1 to correct for multiple comparisons. Compared to HC, PD patients revealed significantly decreased BPnd in the substantia nigra ($p<0.001$; 36.60% difference), caudate ($p=0.042$; 7.90% difference), globus pallidus ($p=0.021$; 12.02% difference), amygdala ($p<0.001$; 32.05% difference), hippocampus ($p<0.001$; 20.64% difference), and thalamus ($p<0.001$; 29.65% difference). We also evaluated voxelwise differences corrected at a clusterwise FDR of 0.05. Widespread decreased BPnd was observed in the striatum, midbrain, locus coeruleus, amygdala, hippocampus, and temporal and parietal cortices. These results support the hypothesis that widespread decrements in $D_{2/3}$ levels are also evident in key mesolimbic regions.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

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Program#/Poster#: 047.23/T9

Topic: C.03. Parkinson’s Disease

Support: DGAPA PAPIIT IT202417

Title: Evaluation of the histological effects caused by a TiO2DA complex in rats whit dopamine depletion model

Authors: *B. I. MEZA AUPART[1,2], P. VERGARA ARAGÓN[2], G. VALVERDE AGUILAR[3], A. SANCHEZ GARCÍA[4], M. PIZARRO RODAS[2], M. GUTIERREZ[2], N. MONTES CRUZ[2]
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Abstract: Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting almost 1% of the population over 65 years. It has not been possible to avoid the progress and the motor complications that characterize it, possibly because these depends of dopamine (DO) decrease in the nigrostriatal pathway. The purpouse of this project was to

implement a method that allows the release of DO; With the intention of reducing the motor alterations that are presented. Mesoporous titanium dioxide (TiO2) complex was synthesized and the pores encapsulated dopamine at predetermined concentrations. In this way, the TiO2-DA complex was obtained, the reddish color of which indicates an instantaneous formation of a charge-transporting complex. It is extremely stable. The effect of the TiO2-DA complex was determined at behavioral level and by histological changes, analyzed using immunohistochemical techniques. Wistar rats (250gr each) were employed and divided into 4 groups (8 each) as follows: 1) Control group, without treatment and with sham surgery; 2) Unilaterally lesioned rats by 6OHDA; 3) Rats unilaterally injured with implant of TiO2 without DO 4) Rats unilaterally injured with implant of the TiO2-DA complex. Each group was evaluated behaviorally; Results showed that there were no significant differences between the group treated with the TiO2-DA complex and the control group. As well as there were no differences between the group of injured rats and the group of rats injured with the implant without DO. It is likely that the continuous release of DO could reverse the motor deficit in the groups of injured rats. This method could be effective as a drug release mechanism for treating PD.

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Poster

047. Dopamine and Non-Dopamine Pathways in Parkinson's Disease Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 047.24/T10

Topic: C.03. Parkinson’s Disease

Title: Neurometabolomic profiling of human *In vitro* models of Parkinson’s disease as a platform for drug development

Authors: C. HILL, K. HA, L. SHANAHAN, S. AKELLA, J. CHAUFTY, J. RANJAN, *R. ROESSLER, S. GESTA, V. VISHNUDAS, P. NARAIN, R. SARANGARAJAN, N. NARAIN, M. KIEBISH
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Abstract: Parkinson’s disease (PD) is a neurodegenerative disorder that primarily and most severely affects midbrain dopaminergic neurons. A variety of cellular and molecular events, such as increased reactive oxygen species, alternations in protein aggregation and neurotransmitter production have been identified as characteristic hallmarks of the disease. Therefore, the ability to measure altered dynamics of neurotransmitter production and breakdown may serve as a potentially useful phenotypic proxy in the drug development process. We performed

metabolomics analysis of well-established *in vitro* models for PD, including SY5Y and NT2 cells, along with patient-specific iPSCs and iPSC-derived neural cell types, at a basal state as well as after exposure to neurotoxins. We developed an LC/MS platform to profile around 100 polar metabolites, which includes neurotransmitters, their precursors and breakdown products, and identified metabolic signatures of neural maturation and neurotoxin exposure. The methodology developed is capable of profiling components of phenylalanine, tyrosine and tryptophan metabolism, as well as the antioxidant glutathione. Using this platform, we demonstrated that the PD *in vitro* models exhibit profound alterations in dopamine biosynthesis and catabolism when exposed to L-DOPA, the standard of care for PD. In particular, metabolites downstream of L-DOPA increase in a dose-dependent manner upon L-DOPA treatment. Furthermore, these models also exhibit altered excretion of dopamine pathway metabolites into the extracellular environment. Altogether, this study demonstrates the importance of metabolomics analysis in disease-specific *in vitro* models of neurodegenerative disorders, specifically PD, for the drug development process.

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Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Program#/Poster#: 048.01/T11

Topic: C.03. Parkinson's Disease

Support: Austrian Science Fund (FWF) W1206-08, P25161 and F4414

Title: Microglial activation and markers of neuroinflammation in a transgenic mouse model of multiple system atrophy: insights into the pathogenesis of selective striatonigral degeneration

Authors: *V. REFOLO[1], S. VENEZIA[1], G. K. WENNING[1], M. ROMERO-RAMOS[2], N. STEFANOVA[1]
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Abstract: It has been widely demonstrated that neuroinflammation plays a pivotal role during the pathogenesis of neurodegenerative diseases. This is also the case for multiple system atrophy (MSA), a disorder belonging to the family of α-synucleinopathies, like Parkinson´s disease and dementia with Lewy bodies. Microglial activation, in particular, represents an especially intriguing actor during these events. Nevertheless, its exact role within disease development still needs to be clarified. This study aims to analyse the progression of neuroinflammatory events over time in a transgenic mouse model of MSA.
We used transgenic mice with C57BL/6 background overexpressing α-synuclein in oligodendrocytes under the proteolipid protein promoter (MSA mice) and wild type C57BL/6 controls of two, five and fifteen months of age. We studied different microglial phenotypes using several immunohistochemical markers and morphological characterization, subdividing the cells in four activation stages (namely A, B, C and D) according to Sanchez-Guajardo et al. (2010). Different brain regions involved in the disease were analysed. We measured inflammatory markers, both in whole mouse brains and in specific brain regions involved in MSA pathology. Two-way ANOVA with variables age and genotype was used for the statistical analysis.
We show early, robust microglial activation in the substantia nigra of MSA mice compared to control animals. No significant genotype-related differences are detected in other regions at any time point. The levels of specific cytokines and chemokines change significantly with aging in the MSA mice, and might contribute to the disease pathogenesis.
Our findings suggest an important role of early, α-synuclein-triggered neuroinflammation for the progressive neurodegeneration of substantia nigra in MSA. The MSA model provides an opportunity for future therapeutic screening targeting neuroinflammation, relevant to the human

disease. Furthermore, our results may prove relevant for the pathogenic mechanisms of related α-synucleinopathies.

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Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Topic: C.03. Parkinson's Disease

Support: NIH T32 Grant 5T32GM109780-02

Michael J Foxx Foundation Target Validation Grant

Title: CNS resident macrophage activation and peripheral immune cell infiltration in an AAV2 α-syn model of Parkinson disease

Authors: *A. M. SCHONHOFF, G. P. WILLIAMS, D. G. STANDAERT, A. N. HARMS
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Abstract: Parkinson disease (PD) is characterized by progressive loss of dopamine producing neurons in the substantia nigra pars compacta (SNpc) and widespread intracellular inclusions of the protein alpha-synuclein (α-syn). Evidence highlights the role of the immune system in progression of PD. In both human patients and rodent models, α-syn pathology is accompanied by microglial activation, T cell infiltration, increased cytokine and chemokine release, and IgG deposition. However, the triggers responsible for initiating this immune response remain poorly understood. Additionally, many previous studies have not separated microglia from CNS resident macrophages (including perivascular, meningeal, and choroid plexus macrophages) and infiltrating cells during analysis, complicating the study of innate mechanisms. To determine the role of resident CNS macrophages in models of PD, we utilized an adeno-associated virus (AAV) that overexpresses full-length human α-syn. We injected this into the SNpc of transgenic mice in which the first exon of CX3CR1 is replaced with GFP. Using flow cytometry and immunohistochemistry, we examined tissue resident CX3CR1+ cells (CD45lo microglia and CD45hi CNS macrophages) for activation markers and proliferation. We found that α-syn led to increased microglial MHCII expression in the midbrain. Additionally, CNS resident macrophages increased in overall number and number of MHCII+ macrophages. Furthermore, α-syn expression led to robust infiltration of peripheral monocytes. These results indicate the importance of microglia and CNS resident macrophages in the initiation of neuroinflammation, recruitment of peripheral immune cells, and neurodegeneration in an α-syn PD model.

Disclosures: **A.M. Schonhoff:** None. **G.P. Williams:** None. **D.G. Standaert:** None. **A.N. Harms:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.03/U1

Topic: C.03. Parkinson's Disease

Support: National Institute on Aging Intramural Research Program

Title: Chronic gut inflammation hastens the onset of motor dysfunction and neuropathology in a mouse model of Parkinson's disease

Authors: ***Y. KISHIMOTO**, W. ZHU, B. DE SOUSA SILVA, J. SEN, M. P. MATTSON
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Abstract: In addition to the motor symptoms related to degeneration of midbrain dopaminergic neurons, many patients with Parkinson's disease (PD) have symptoms of gastrointestinal dysfunction. Recent findings suggest that the alpha-synuclein pathology that typifies neurons affected in PD may occur first in the enteric nervous system and then propagate retrogradely to the brainstem via the vagus nerve. We previously reported that a pro-inflammatory diet exacerbated vagus nerve dysfunction, whereas an anti-inflammatory diet ameliorated this dysfunction in transgenic mice overexpressing mutant alpha-synuclein (A53T) in neurons (PD mice). Here, we tested the hypothesis that chronic low-level intestinal inflammation can accelerate PD symptoms and pathology in PD mice. Beginning at 3 months of age, wild type (WT) and PD mice were given either normal drinking water or water containing 0.5% (w/v) dextran sodium sulfate (DSS), which induces gut inflammation and cannot cross the blood brain barrier. Mice were monitored every 2 weeks for motor dysfunction and at the end of 12 weeks of treatment animals were sacrificed for pathological investigation. PD mice treated with DSS had symptoms of motor dysfunction 2 months earlier and had more severe PD pathology (alpha-synuclein accumulation in gut and brain and dopaminergic cell loss at substantia nigra) than PD mice treated with water alone. DSS treatment resulted in chronic low level ulcerative colitis-like gut histopathological changes in both WT and PD mice. Proinflammatory cytokines were increased in the colons of both DSS treated WT and PD mice. However, only PD mice treated with DSS had increased levels of proinflammatory cytokines in the brain. This finding was validated by the presence of microglia activation in the brains of PD mice treated with DSS. Interestingly, in serum there was no change in the levels of proinflammatory cytokines and the presence of alpha-synuclein could not be detected. Together, this suggests that chronic gut inflammation accelerates PD pathogenesis and that this may occur via retrograde propagation of

alpha-synuclein pathology from the gut to the brain via the enteric nervous system. Supported by the NIA Intramural Research Program.

Disclosures: Y. Kishimoto: None. **W. Zhu:** None. **B. de Sousa Silva:** None. **J. Sen:** None. **M.P. Mattson:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.04/U2

Topic: C.03. Parkinson's Disease

Support: 1T32 HD071866

P20 NS095230

Title: Induction of activated T cells in brain and peripheral lymph nodes in an AAV synuclein model of Parkinson disease

Authors: *G. WILLIAMS, A. SCHONHOFF, A. HARMS, D. STANDAERT
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Abstract: Alpha-synuclein (α-syn) accumulation is a hallmark of Parkinson disease (PD). Recently, this accumulation has been shown to lead to an immune response producing a pro-inflammatory environment in the CNS which includes infiltration of CD4 and CD8 T cells. In other CNS inflammatory disorders such as MS, the infiltration of activated T cells into the brain and spinal cord after priming in peripheral lymph nodes is important for the initiation and progression of the disease process. We sought to determine whether a similar process was at work in PD. Using an adeno associated virus (AAV) to over-express α-syn in mice and a combination of immunohistochemistry and flow cytometry, we examined the effect of abnormal brain α-syn on brain and lymph node T cell populations. AAV expressing either full-length human α-syn or GFP as a control was injected into the substantia nigra of mice. T cell populations were assessed in the brain and lymph nodes four weeks later. We found that *in vivo,* overexpression of full-length human α-syn does indeed induce substantial infiltration of activated CD3/TCR+ T cells into the substantia nigra, an effect not seen with the AAV-GFP control virus. Additionally, we observed an increase in activated CD44+ CD4 and CD8 T cells in the deep cervical lymph nodes which drain from the CNS in response to α-syn. These observations suggest that overexpression of α-syn in the brain leads to an immune response that involves α-syn dependent priming of T cells in the lymph nodes and subsequent migration into the brain parenchyma. Better understanding of this T cell response could lead to more targeted and effective immunotherapies to stop or slow the progression of PD.

Disclosures: **G. Williams:** None. **A. Schonhoff:** None. **A. Harms:** None. **D. Standaert:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.05/DP03/U3 (Dynamic Poster)

Topic: C.03. Parkinson's Disease

Support: Research Foundation Flanders, postdoctoral fellowship to LDG

KU Leuven research council, C3 project to LM

Title: The eye as a window to the brain: *In vivo* imaging of Parkinson's disease processes in the retina

Authors: *L. DE GROEF[1], L. VEYS[2], L. ANDRIES[2], E. LEFEVERE[2], C. VAN DEN HAUTE[2], V. BAEKELANDT[2], L. MOONS[2]
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Abstract: Accumulating evidence suggests that, rather than trying to access information about the disease state of the CNS in the brain, one could exploit the unique properties of the eye. *In vivo* assessments of retinal structure, electrophysiological function, and performance of vision-driven tasks, have revealed specific signs of deterioration in Parkinson's disease (PD) patients and animal models. In this study, we exploit the advantages of the retina as a model organ for CNS research, and put forward two objectives: (i) the characterization a novel mouse model for the study of PD in the retina, based on local, viral vector-mediated overexpression of alpha-synuclein (aSYN); and (ii) development of an integrated workflow for *in vivo* examination of retinal neurodegeneration, inflammation, and protein aggregation.
Intravitreal delivery of an rAAV2/2mut(Y444F)-CMV-h[A53T]aSYN viral vector resulted in retinal aSYN overexpression in inner retinal neurons at 2 weeks post injection. At week 14, confocal scanning laser ophthalmoscopy showed autofluorescent aSYN aggregates; and optical coherence tomography revealed a significantly reduced thickness of the total retina and the inner nuclear layer at week 14 and 18, as compared to baseline values. A significant decrease in visual acuity was measured by optomotor test, at week 14 to 18 post vector injection. Together, these results suggest that the retina can be used as a model organ to study the effect of (or the link between) a-synucleinopathy on neuronal survival. Additional experiments, looking into electrophysiological function, single-cell imaging of apoptosis and inflammation, and extra behavioral read-outs of visual function, are currently being performed.
In conclusion, by combining readouts from longitudinal *in vivo* follow-up, we are creating an integrated view on the impact of a-synucleinopathy on retinal histology, (electro)physiology and visual function. We believe that, with this retinal PD model and workflow, we will be able to

provide valuable research tools to gather new insights into the disease mechanisms of PD, to perform preclinical drug development, and to reduce the number of animals needed for PD research.

Disclosures: L. De Groef: None. **L. Veys:** None. **L. Andries:** None. **E. Lefevere:** None. **C. Van Den Haute:** None. **V. Baekelandt:** None. **L. Moons:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.06/U4

Topic: C.03. Parkinson's Disease

Support: CAMS Initiative for Innovative Medicine 2016-12M-1-008

Title: JZ101 deficiency exhibits behavioral & cognitive impairments & α-synucleinopathy

Authors: *J. YANG, F. GAO, C. LI, H. WANG, H. CHEN, Y. HU, J. ZHANG
Peking Union Med. Col., Beijing City, China

Abstract: Parkinson's disease (PD) is the most common neurodegenerative movement disorder, which is characterized by the massive loss of midbrain dopaminergic neurons and abundant intracellular α-synuclein (α-syn) neuronal inclusions. Our previous study demonstrated that JZ101 was neuroprotective and absence of JZ101 resulted in deficits in learning and memory. However, the role of JZ101 in PD is still unknown. Here, we show a role for JZ101 in regulation of PD progression. Remarkably, mice lacking JZ101 in the forebrains resulted in substantial neurodegeneration in the forebrains accompanying typical α-synucleinopathy with high level of immunostaining for phosphorylated (Ser129) α-syn (pS129-α-syn), the formation of pathogenic fibrillar aggregates. While accumulation of oligomeric α-syn is neurotoxic, mice with specific depletion of JZ101 in in the forebrains exhibited significant higher levels of high-molecular-weight pS129-α-syn including dimer, trimer, tetramer, and oligomer compared to WT littermates. In addition, the Tyrosine hydroxylase (TH)+ fiber density and the TH+ dopaminergic neurons at the substantia nigra pars compacta were decreased significantly in JZ101 conditional knockout mice compared to WT mice by immunohistochemical staining. In conclusion, this study confirmed that specific deletion of JZ101 causes PD-like deficits, including loss of dopaminergic neurons and accumulation of α-synuclein, and our studies would give a new implication for PD therapy.

Disclosures: J. Yang: None. **F. Gao:** None. **C. Li:** None. **H. Wang:** None. **H. Chen:** None. **Y. Hu:** None. **J. Zhang:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Program#/Poster#: 048.07/U5

Topic: C.03. Parkinson's Disease

Support: NINDS Grant R15NS093539

Hillman Foundation Grant 109033

Title: Influence of aging and gender in a mouse model of limbic alpha-synucleinopathy in Lewy body disorders

Authors: *D. MASON[1], K. M. MINER[2], T. N. BHATIA[2], M. A. CARCELLA[2], R. K. LEAK[3], K. C. LUK[4]
[1]Dept. of Pharm., [3]Pharmacol., [2]Duquesne Univ., Pittsburgh, PA; [4]Dept of Pathology and Lab. Med., Univ. Pennsylvania, Philadelphia, PA

Abstract: Parkinson's disease and dementia with Lewy bodies are both characterized by the early emergence of Lewy inclusion bodies in olfactory structures and loss of smell years before the onset of movement deficits. Lewy bodies are partly composed of aggregated, fibrillar α-synuclein protein. Previously, we developed a model of Lewy body disorders by injecting preformed α-synuclein fibrils into the mouse olfactory bulb/anterior olfactory nucleus (OB/AON). Within three months, Lewy-like inclusions were formed in the OB/AON and limbic areas that project directly to the site of infusion (amygdala, piriform and entorhinal cortices, hippocampus proper, and subiculum), as confirmed with the tract-tracer FluoroGold. Here we examined the influence of aging and gender on the same model, as Lewy body disorders are more common in men and the elderly. α-synuclein fibrils were infused in young 3 month-old male and female mice and in middle-aged 11 month-old male mice. Fibril infusions increased the latency to locate buried food in young and middle-aged males but not in young females. However, fibril infusions increased the latency to contact one wooden block harboring a novel animal odor (out of multiple blocks with familiar animal odors) and the fraction of time spent contacting a block with a novel synthetic odor in young females but not in the males. Middle-aged males spent dramatically more total time smelling blocks with any odor than young males, but fibril infusions reduced the size of this effect. Spontaneous forelimb contacts with the walls of a cylinder were reduced in fibril-infused young males and females—but not middle-aged males—relative to PBS-infused controls. There was no significant influence of fibrils, age, or gender on the novel object and novel place recognition memory tests by 5 months post-infusion. Notably, 5 out of 16 middle-aged fibril-infused males died by six months post-infusion, compared to only 1 out of 16 PBS-infused middle-aged males. None of the young males died and only 1 female out of 8 was lost in each of the PBS and fibril groups. Limitations of this study

include that the behavioral assays (other than for olfaction) were only performed once and that middle-aged females were not included. Histological studies are still underway.

Disclosures: D. Mason: None. **K.M. Miner:** None. **T.N. Bhatia:** None. **M.A. Carcella:** None. **R.K. Leak:** None. **K.C. Luk:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.08/U6

Topic: C.03. Parkinson's Disease

Title: TUDCA inhibits autophagy via LAMP-1 in a chronic mouse model of Parkinson's disease

Authors: *E. CUEVAS[1], N. P. GÓMEZ-CRISÓSTOMO[2], C. ESCUDERO-LOURDES[3], H. ROSAS-HERNANDEZ[1], S. LANTZ[1], J. RAYMICK[1], M. G. PAULE[1], S. SARKAR[1]
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Abstract: Parkinson's disease (PD) is a progressive motor disease, the main hallmark of which is selective degeneration of dopaminergic (DA) neurons. The molecular mechanism underlying the etiology of PD is unknown. The administration of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in rodents mimics Parkinson' disease and it is used to study the possible molecular pathways involved in PD and to look for molecules with neuroprotective activity that may have potential in PD therapy. Tauroursodeoxycholic acid (TUDCA) is a molecular chaperone which modulates cell death by interrupting classic pathways of apoptosis and acts as a mitochondrial membrane stabilizer and recently, it has been suggested that TUDCA might be protective in a mouse model of MPTP-induced toxicity but the mechanisms involved in this protection are not fully understood. The aim of this study was to evaluate the role of autophagy in MPTP-induced toxicity and to determine if TUDCA can prevent autophagic damage. Mice were divided into three groups: 1) Control (Saline/Probenecid [250mg/kg]); 2) MPTP (MPTP-P [25mg/kg + Probenecid, 250mg/kg]); and 3) TUDCA (200 mg/kg) + MPTP-P and received the corresponding treatment for 10 days. Western Blot (WB) markers of autophagy and immunohistochemical (IHC) markers of dopaminergic cells and glial were analyzed. MPTP-induced autophagy was associated with increased lysosome-associated membrane protein 2 (LAMP1) expression and increased α-synuclein aggregation. MPTP decreased tyrosine hydroxylase and dopamine transporters as indicators of dopaminergic damage and induced microglial and astroglial activation. Pretreatment with TUDCA prevented autophagy, inhibited α-synuclein aggregation, protected dopaminergic neuronal damage and prevented the microglial and astroglial activation caused by MPTP. Together, these results suggest that: 1) autophagy may

be involved in PD; 2) TUDCA can modulate the effects of MPTP; and 3) TUDCA may be a novel candidate for PD therapy.

Disclosures: E. Cuevas: None. **N.P. Gómez-Crisóstomo:** None. **C. Escudero-Lourdes:** None. **H. Rosas-Hernandez:** None. **S. Lantz:** None. **J. Raymick:** None. **M.G. Paule:** None. **S. Sarkar:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Topic: C.03. Parkinson's Disease

Support: DOD W81XVVH-12-1-0051

Title: Axonopathy, autophagy and mitochondrial abnormalities in a mouse model of human wild type alpha synuclein overexpression

Authors: *A. P. TAGLIAFERRO, T. KAREVA, N. KHOLODILOV, R. E. BURKE
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Abstract: Alpha-synuclein (α-syn) is the major component of Lewy bodies, a histopathological hallmark for Parkinson's disease (PD) and it is involved in both sporadic and familial cases of the disease. Point mutations and whole locus multiplications in the α-syn gene cause autosomal dominant PD (Hardy et al., 2006). Previously, we have used an adeno-associated viral vector (AAV) construct which carries human (h) wild type α-syn under the neuron-specific synapsin-1 promoter to investigate the effects of hα-syn overexpression in the mouse nigrostriatal dopaminergic (DA) system. We demonstrated that α-syn overexpression induces the appearance of axonal swellings and spheroids in DA fibers and a decrease in the optical density (OD) of tyrosine hydroxylase (TH) expression in the dorsolateral striatum at 4 weeks after AAV injection. These early signs of axonopathy are followed by a decrease in the number of DA axons in the medial forebrain bundle (MFB) and in the number of TH positive (+) neurons in the substantia nigra (SN) at 8 weeks after AAV delivery (Tagliaferro et al., SFN 2016). Here we investigate the persistence of these effects at 16 weeks and we seek to identify the cellular events associated with the appearance of axonopathy at 4 weeks. Adult mice (2 months old) received unilateral intranigral injection of either AAV2/7-α-syn or AAV2/7-tomato (used as a control protein). At 16 weeks, the OD of TH immunostaining in the striatum was reduced by about the same amount observed at 8 weeks. At 4 weeks after AAV, although abundant hα-syn expression was observed in the soma and nucleus of TH+ neurons, we did not observe α-syn aggregates. Evidence of autophagy in axons was demonstrated by the observation of LC3-GFP –positive puncta and spheroids at the confocal microscopy level. The presence of autophagic vacuoles in

axons was confirmed at the ultrastructural level. At 4 weeks ultrastructural studies also showed the presence of abnormal mitochondria in dendrites located in the SN. They were greatly enlarged, there was obliteration of the cristae, and the appearance of multilobular profiles, suggestive of fission. These data indicate that hα-syn overexpression induces degeneration of the nigrostriatal DA system and that this is an effective mouse model that recapitulates some of the most important histopathological hallmarks of PD.

Disclosures: A.P. Tagliaferro: None. **T. Kareva:** None. **N. Kholodilov:** None. **R.E. Burke:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Topic: C.03. Parkinson's Disease

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Instituto de Salud Carlos III PI13/01390 co-financed by the European Regional Development Fund "A way to build Europe"

Title: Short- and long-term memory impairment in mice overexpressing alpha- and gamma-synuclein in the dopamine neurons. Implication in Parkinson' disease

Authors: R. PAVIA-COLLADO[1], D. ALARCÓN-ARÍS[1], E. RUIZ-BRONCHAL[1], F. ARTIGAS[2], *A. BORTOLOZZI[3,4]
[1]IDIBAPS-IIBB(CSIC), Barcelona, Spain; [2]IIBB(CSIC)-IDIBAPS-CIBERSAM, Barcelona, Spain; [3]IIBB-CSIC, Barcelona, Spain; [4]IDIBAPS-CIBERSAM, Barcelona, Spain

Abstract: Idiopathic Parkinson's disease (PD) is characterized by progressive brain pathology affecting multiple neurotransmitter systems, leading to a diverse profile of autonomic, motor, cognitive and psychiatric dysfunctions. Multiple convergent lines of evidence implicate the aggregation and accumulation of α-synuclein in the PD pathogenesis. Moreover, post-translational changes of γ-synuclein increase the α-synuclein aggregation. α- and γ-Synuclein are members of the synuclein family of small cytoplasmatic neuron-specific proteins, and have been suggested to modulate the function of monoamine transporters (DAT, SERT). We previously reported that α-synuclein knockdown mice showed increased extracellular DA and 5-HT levels-compard to control mice- in caudate-putamen (CPu) and medial prefrontal cortex (mPFC) after

DAT or SERT blockade with nomifensine or citalopram, respectively (Alarcón-Arís et al., in review). Given the role of monoamine neurotransmission in cognitive processes, in the present study we assessed the effects of over-expressing α- and γ-synuclein in DA neurons on short- and long-term spatial memory. We generated a mouse model overexpressing the human wild-type α- or γ-synuclein in DA neurons from the substantia nigra compacta (SNc) and ventral tegmental area (VTA) using an adeno-associated virus type-5 (AAV5)-α-synuclein or AAV10-γ-synuclein, unilaterally injected in SNc/VTA. AAV5-α-synuclein mice showed increased human α-synuclein mRNA levels in the ipsilateral SN over time, reaching a 278% of sham mice at 8 weeks post-infection. Similarly, AAV10-γ-synuclein mice reached to a maximal of 250% of sham mice. Overexpression of α- or γ-synuclein led to lower extracellular DA levels in CPu and mPFC compared to sham mice after local veratridine (50μM) or nomifensine (1-10-50μM) administration at 4-week post-infection. Moreover, overexpression of α- or γ-synuclein led to the impairment of working memory in mice, as revealed by passive avoidance and novel object recognition tests at 4-8 weeks post-infusion. Likewise, these mice showed deficits in the spatial learning using the Morris water maze. These non-motor symptoms appeared earlier than motor deficits assessed by the cylinder test and rotarod. Overall, these findings indicate that that 1) α- and γ-synuclein are directly involved in the regulation of cognitive functions, likely through changes in monoamine function, and 2) overexpression of α- or γ-synuclein in DA neurons mimics the temporal progression of clinical symptoms in PD, with early cognitive deficits appearing before motor symptoms.

Disclosures: R. Pavia-Collado: None. **D. Alarcón-Arís:** None. **E. Ruiz-Bronchal:** None. **F. Artigas:** None. **A. Bortolozzi:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.11/U9

Topic: C.03. Parkinson's Disease

Title: Alpha-synuclein induces modulation of mitogen activated protein kinase p38 gamma

Authors: *M. IBA, C. KIM, E. MASLIAH
Lab. of Neurogenetics, Exptl. Neuropathology section, Natl. Inst. on Aging, NIH, Bethesda, MD

Abstract: Aggregation of presynaptic protein, alpha-synuclein (α-syn) is a hallmark of neurodegenerative diseases such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy. A recent study (Ittner et al., 2016) suggested that one of the mitogen activated protein kinase (MAPK) p38 gamma (p38γ) in neurons plays an important role on Alzheimer's disease (AD) pathogenesis by phosphorylating tau at an specific site which reduced amyloid-β toxicity. Although regulation of p38γ in AD became clear, the role of MAPK

p38γ in alpha-synucleopathy have not been studied. To investigate whether p38γ is involved in alpha-synucleopathy, we analyzed human wild type α-syn overexpressing transgenic (Tg: Thy1 promoter line 61) and its littermate non-transgenic mice (non-Tg) as well as brains from patients with DLB/PD. Immunohistochemical analysis revealed that p38γ was localized to synaptic terminals in non-Tg mice, whereas in Tg mice immunostaining in the synaptic terminals was reduced, and redistribution to the neuronal cell bodies was observed. Further, double staining showed that p38γ staining were co-localized with α-syn aggregates in Tg mice compared to non-Tg mice. Further biochemical analysis confirmed a significant reduction of p38γ in Tg mice compared to non-Tg mice. Additional studies are underway in other models of synucleinopathy as well as in the brains of DLB/PD patients. The mechanisms through which α-syn might dysregulate p38γ are unclear however transcriptional and post-translational alterations might play a role. These results suggest that the MAPK p38γ pathway is modulated by the presence of α-syn and might play a role in the mechanisms of synaptic dysfunction in DLB/PD.

Disclosures: M. Iba: None. **C. Kim:** None. **E. Masliah:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.12/U10

Topic: C.03. Parkinson's Disease

Title: Sirtuin3 regulates mitochondrial dynamics in α-synuclein-induced loss of mitochondrial function

Authors: *J.-H. PARK, M. DELENCLOS, A. FAROQI, N. DEMEO, P. J. MCLEAN
Dept. of Neurosci., Mayo Clin., Jacksonville, FL

Abstract: The sirtuins are highly conserved nicotinamide adenine dinucleotide (NAD^+)-dependent enzymes that have beneficial effects against neurodegenerative diseases. Mitochondrial sirtuins, especially sirtuin3 (SIRT3), play a major role in maintaining mitochondrial integrity, metabolism, and homeostasis by regulating different aspects of the organelles' processes. Here, we studied a protective role of SIRT3 in Parkinson's disease (PD) and provide mechanistic insight into the interaction between SIRT3 and α-synuclein (αS), the major component of the hallmark neuronal inclusions in PD. We found that an increase in αS oligomers induces SIRT3 downregulation, leads to increased expression of phospho-DRP1 (Ser616), and recruitment of dynamin-related protein 1 (DRP1), a member of the dynamin family of large GTPases, on the mitochondrial outer membrane. The increase of αS oligomers is accompanied by a decrease in optic atrophy 1 (OPA1), thus driving mitochondria dynamics toward fission and fragmentation. Interestingly, expression of SIRT3, OPA1, and DRP1 is significantly decreased in a rat viral vector model of αS-induced neurodegeneration.

Mitochondrial respiration was assessed using the Agilent Seahorse to measure key parameters of mitochondrial function including oxygen consumption rate (OCR) of cells. Our results show that OCR of basal respiration, ATP production, maximal respiration, and spare respiratory capacity are all significantly decreased in cells overexpressing αS oligomers. Treatment with the AMP-activated protein kinase (AMPK) agonist AICAR (5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside) restored SIRT3 and OPA1 expression, and inhibited phospho-DRP1 and αS oligomer formation, with a concomitant improvement in mitochondrial function. Taken together these data suggest that increasing SIRT3 levels rescues αS-induced mitochondrial dysfunction by regulating mitochondrial fission and fusion. These studies provide mechanistic understanding of the protective role of a mitochondrial fidelity protein, SIRT3, in mitochondrial dysfunction with the potential application as a novel target for pharmacological strategies in mitochondrial-associated neurodegenerative disorders, including PD.

Disclosures: J. Park: None. **M. Delenclos:** None. **A. Faroqi:** None. **N. DeMeo:** None. **P.J. McLean:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

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Program#/Poster#: 048.13/U11

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation

Title: Testing the effect of retention in endoplasmic reticulum (RER1) on synucleinopathy in a mouse model of Parkinsonism

Authors: *M. S. PARMAR[1], H.-J. PARK[2], D. RYU[1], K. N. MCFARLAND[1], J. JOSEPH[2], R. FOELS[2], L. POWELL[2], S. ANAGNOSTIS[2], N. R. MCFARLAND[1]
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Abstract: Alpha-Synuclein (αSyn) is a major component of Lewy bodies found pathologically in Parkinson disease (PD) and related synucleinopathies. Abnormal accumulation of αSyn is linked to endoplasmic reticulum (ER) stress, defective intracellular protein/vesicle trafficking, and cytotoxicity. Targeting factors involved in ER-related protein processing and trafficking may be a key to modulating αSyn levels and associated toxicity. Retention in endoplasmic reticulum 1 (RER1) has recently been identified as an ER retrieval/retention factor that plays a role in regulating ER-Golgi trafficking of Alzheimer's disease-related proteins. As αSyn accumulates pathologically in the ER, we hypothesized that RER1 may help to regulate αSyn trafficking and levels. Co-expression of RER1 and αSyn in HEK293 and H4 cells significantly decreases αSyn levels. RER1 effects are specific to αSyn and dependent on the αSyn NAC region. We have

further demonstrated that RER1 localizes to αSyn-positive Lewy bodies in Dementia with Lewy body cases. Together, these findings provide evidence that RER1 may be an important mediator of αSyn. In this study, we tested the effect of viral expression of RER1 *in vivo* on toxicity in a transgenic mouse model of PD. Recombinant AAV8 expressing RER1, RER1Δ25, or EGFP were injected intracerebroventricularly (ICV) into newborn (P0), transgenic heterozygote M83 mice that express A53T-αSyn. At 8 weeks of age, mice then received the bilateral intrastriatal injections of mouse αSyn preformed fibrils (PFF) to induce synucleinopathy. Ten weeks post PFF injection, pole test, rotarod, and SHIRPA were performed and animals sacrificed to collect brain regions for biochemistry and immunohistochemistry. No significant difference was observed with an average time to descend (pole test) between PFF injected control (EGFP) and RER1 group. In brain regions (Cortex, Thalamus, and Midbrain/Brain stem), no reduction in αSyn and 81A (pathological insoluble pSer129 αSyn) was observed in the RER1 as compared to control group. The findings may be associated with limited viral expression of RER1 in the midbrain region, limiting the effect on the spread of αSyn pathology in other regions. Although preliminary, these findings do not support a role for RER1 in mitigating "seeding" and synucleinopathy in a transgenic model of Parkinsonism. Future studies should optimize somatic brain expression to better target synucleinopathy in this mouse model and levels of RER1 expression to better test the effects of RER1 on αSyn levels, aggregate formation, and toxicity.

Disclosures: **M.S. Parmar:** None. **H. Park:** None. **D. Ryu:** None. **K.N. McFarland:** None. **J. Joseph:** None. **R. Foels:** None. **L. Powell:** None. **S. Anagnostis:** None. **N.R. McFarland:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.14/U12

Topic: C.03. Parkinson's Disease

Support: NRF2016R1C1B1011117

Title: Alpha-synuclein interferes GSK3β/β-catenin signaling pathway through proteinphosphatase 2A inactivation

Authors: *J. LIM[1], S. KIM[2], H. CHOI[2]
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Abstract: Alpha-synuclein (α-SYN) is expressed during neuronal development and is mainly involved in the modulation of synaptic transmission. Missense mutations and amplifications of this gene have been associated with the pathogenesis of Parkinson's disease. Here, we evaluate whether α-SYN plays a detrimental role in the phenotypic and morphological regulation of

neurons. We also identify the underlying mechanisms of this process in all-trans-retinoic acid (RA)-induced differentiated SH-SY5Y cells, which represents dopaminergic (DAergic) phenotype. Our results indicate that overexpression of wild-type or mutant A53T α-SYN attenuated the RA-induced upregulation of tyrosine hydroxylase and dopamine transporter as well as neurite outgrowth in SH-SY5Y cells. In addition, GSK-3β inactivation and downstream β-catenin stabilization were associated with RA-induced differentiation, which was attenuated by α-SYN. Moreover, protein phosphatase 2A was positively regulated by α-SYN and was implicated in the α-SYN-mediated interference with RA signaling. The results obtained from SH-SY5Y cells were verified in primary cultures of mesencephalic DAergic neurons from A53T α-SYN transgenic mice, which represent high levels of α-SYN and protein phosphatase 2A in the midbrain. The number and length of neurites in tyrosine hydroxylase-positive as well as Tau-positive cells from A53T α-SYN transgenic mice were significantly lower than those in littermate controls. The current results provide novel insight into the role of α-SYN in the regulation of neuronal differentiation, including DAergic neurons. Identifying the signaling pathway involved in the α-SYN-mediated dysregulation of neuronal differentiation could lead to a better understanding of the developmental processes underlying α-SYN-related pathologies and facilitate the discovery of specifically targeted therapeutics.

Disclosures: **J. Lim:** None. **S. Kim:** None. **H. Choi:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Topic: C.03. Parkinson’s Disease

Support: Biomedical Laboratory Research & Development Service of the VA Office of Research and Development Award Number I01 BX001641

NIH grant P30 AG013319-21

Title: Elevated levels of the dopamine metabolite 3,4-dihydroxyphenylacetaldehyde exacerbates motor deficits in an alpha-synuclein mouse model of Parkinson's disease

Authors: ***P. A. MARTINEZ**[1,2], V. MARTINEZ[2], E. FERNANDEZ[3,2,4], R. STRONG[3,2,5]
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Abstract: Parkinson's disease (PD) is second most common neurodegenerative disease affecting ~1-2% of individuals over the age of 65 years. Neurodegeneration of dopaminergic neurons in the nigrostriatal pathway results in a reduction of striatal dopamine (DA) that is causally related to impaired motor function. A pathological hallmark of PD, is the presence of alpha-synuclein (αSyn)-rich Lewy bodies in surviving DA neurons. While it remains unclear what mechanism(s) underlies the selective vulnerability of DA neurons, a growing body of evidence implicate the dopamine metabolite, 3,4-dihydroxyphenylacetaldehyde (DOPAL). DOPAL is the first product of dopamine catabolism by the enzyme monoamine oxidase. We previously reported that deletion of the two aldehyde dehydrogenase (ALDH) enzymes (Aldh1a1 and Aldh2) that are responsible for the detoxification of DOPAL, results in elevated levels of DOPAL, degeneration of tyrosine hydroxylase-immunoreactive neurons and deficits in motor performance. Additionally, mutations or multiplication of the SNCA gene which encodes for the principal component of Lewy bodies, αSyn, implicates αSyn in PD. Evidence suggests αSyn undergoes aggregation to form neurotoxic oligomers. DOPAL promotes and stabilize αSyn oligomers. The selective generation of DOPAL in DAergic neurons and its ability to stabilize neurotoxic αSyn oligomers, led us to hypothesize that, αSyn is mechanistically related to the neurochemical and behavioral manifestations of PD that result from elevated DOPAL. To test this hypothesis, we generated mice deficient in Aldh1a1 and Aldh2 crossed them to mice that overexpress the human wildtype αSyn. We found that overexpression of αSyn in the presence of elevated levels of DOPAL was associated with exacerbation of deficits in motor performance. The results of neurochemical assays will be discussed.

Disclosures: P.A. Martinez: None. **V. Martinez:** None. **E. Fernandez:** None. **R. Strong:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Program#/Poster#: 048.16/V2

Topic: C.03. Parkinson's Disease

Support: NIH 5P20 GM103653

Title: The SUMO conjugase Ubc9 regulates the stability of alpha-synuclein in Parkinson's disease models

Authors: *Y.-H. KIM, E. CARTIER, J. VIANA, D. WILLIAMS
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Abstract: Post-translational modification (PTM) has been addressed as a key regulatory mechanism for modulating protein aggregation/degradation in neurodegeneration. However, a

form of PTM, Small Ubiquitin Modifier (SUMO) has not been well characterized in Parkinson's disease (PD) pathology. Although SUMOylation may increase the solubility of alpha-synuclein, SUMOylated alpha-synuclein has been identified in the halo of Lewy bodies. Thus, it is still unclear in understanding the role of SUMOylation in alpha-synuclein in dopaminergic neurons. Here, we assess the role of SUMO conjugase, Ubc9 as a critical post-translational modifier to regulate the solubility, stability, and degradation of alpha-synuclein in dopaminergic cells *in vitro* and mouse brain. The objective of this study is to assess SUMOylation as a novel regulatory target for preventing alpha-synuclein mediated protein aggregation in dopaminergic neurons. This implies that pathological changes in the SUMOylation of alpha-synuclein may lead to alterations in acute regulation of protein (mis)folding or aggregation, which is key to the neuropathology of PD. We identified that SUMO1 is constitutively conjugated to alpha-synuclein in rat dopaminergic N27 cells and mouse striatum and midbrain. Our *in vitro* preliminary results demonstrate that Ubc9 over-expression protects the N27 cells against MPP+ induced oxidative stress and increases the protein half-life of alpha-synuclein, probably via the inhibition of proteasome and lysosome without impacting its transcription. In addition, knocking-down the endogenous Ubc9 using RNAi reduces the level of alpha-synuclein in N27 cells. Moreover, in the MPTP-lesioned mice, the chronic treatment substantially reduces the level of SUMO1 conjugated to alpha-synuclein in the mouse striatum. This suggests that pathological alterations in the SUMOylation of alpha-synuclein may cause the protein (mis)folding or aggregation. Therefore, SUMOylation of alpha-synuclein and other PD-related proteins can be potential therapeutic targets for preventing Lewy body induced neurodegeneration such as PD and Dementia with Lewy bodies (DLB).

Disclosures: Y. Kim: None. **E. Cartier:** None. **J. Viana:** None. **D. Williams:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.17/V3

Topic: C.03. Parkinson's Disease

Title: Characterization of alpha-synuclein and neurotransmitters during the sleep wake cycle of a Parkinson's disease model expressing human wild-type alpha-synuclein

Authors: *H. B. JANSSENS, L. YU, T. CREMERS, A. RASSOULPOUR
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Abstract: Alpha-synuclein protein (aSYN) is hypothesized to be involved in the pathophysiology of Parkinson's (PD) - a neurodegenerative disorder effecting motoric symptoms. However, non-motor symptoms in PD patients including sleep disturbances, cognitive decline, depression and anxiety can occur years prior to PD onset, suggesting a lengthy

pre-symptomatic period and compensatory neural mechanisms. Therefore, we set out to examine the levels of aSYN and neurotransmitters (dopamine, norepinephrine, serotonin, glutamate, GABA, and acetylcholine) at various ages of male hemizygous (Tg) mice of Line 15, Tg(Thy1-SNCA)15Mjff/J (JAX) at ages 9, 12 and 18 months. To this end, *in vivo* microdialysis was carried out in Tg mice. Male C57Bl/6 strain (WT) were used for controls at age 12 months. The levels of aSYN were determined in dialysate samples by ELISA analysis, and neurotransmitters were measured by LC MS/MS. Results showed basal aSYN levels in Tg mice are similar among ages 9, 12 and 18 months. Interestingly, we found that aSYN increased during the dark (active) phase with older Tg animals trending higher levels. Of the neurotransmitters examined, we found that the levels of dopamine, GABA and glycine levels are higher in older animals compared to younger Tg animals. These results demonstrate a significant variation in aSYN during the light vs dark cycle of Tg mice. Given the lack of change in DA, Glu, 5HT, NE, GABA, and ACh levels in Tg vs WT animals and the sleep disturbances associated with PD symptoms, the current results implicate aSYN as a possible mediator of sleep.

Disclosures: H.B. Janssens: None. **L. Yu:** None. **T. Cremers:** None. **A. Rassoulpour:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.18/V4

Topic: C.03. Parkinson's Disease

Title: Administration of aav alpha-synuclein to c57 and g2019s mice

Authors: R. HODGSON[1], J. KURKIPURO[1], T. PARKKARI[1], T. N. MARTINEZ[2], M. J. FELL[3], *T. HEIKKINEN[1], L. A. HYDE[3], A. J. NURMI[1], T. A. LANZ[4], A. STEPAN[4], M. A. BAPTISTA[2]
[1]Charles River Discovery, Kuopio, Finland; [2]Michael J. Fox Fndn., New York, NY; [3]Merck & Co. Inc., Boston, MA; [4]Pfizer Inc, Cambridge, MA

Abstract: AAV induced overexpression of A53T alpha synuclein has been used as an animal model for Parkinson's disease research. The vast majority of this research has been done in rats with some work in primates; however relatively little has been done to characterize the analogous treatment in mice. There are significant advantages to working in mouse models including reduced cost of the animals, reduced drug requirement for pharmacological studies and access to a wide array of transgenic animals. The purpose of the present study was to assess the effect of unilateral delivery of AAV 2/1 alpha-synuclein (1.7×10^{12}vg/mL) in C57 mice on TH and dopamine. Four weeks following infusion, we found a robust increase in alpha synuclein in the substantia nigra in the infused hemisphere but only a very modest decrease in TH and no significant change in DA or its metabolites in the infused hemisphere relative to the non-infused

hemisphere. Previous research in rats has shown that, relative to WT animals, LRRK2 overexpressing rodents are more sensitive to AAV alpha synuclein induced effects. We therefore infused G2019S mice with AAV alpha synuclein and compared the effects to their WT counterparts. The G2019S mice demonstrated a modest, but not statistically significant, decrease in TH, but an increase in DA content that was more robust at 4 weeks than 8 weeks. Compared to similar AAV alpha synuclein treatment in rats, these results in mice are much less robust. These findings clearly demonstrate that the mouse is less sensitive to AAV alpha synuclein treatment than rats. Further work testing higher titers in mice will be necessary to assess the viability of AAV alpha synuclein treated mice as a tool in Parkinson's disease research.

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Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.19/V5

Topic: C.03. Parkinson's Disease

Title: Administration of AAV alpha synuclein in SD and G2019S-LRRK2 rats

Authors: R. HODGSON[1], T. PARKKARI[1], T. N. MARTINEZ[2], M. J. FELL[3], L. KOISTINEN[1], T. HUHTALA[1], J. RYTKÖNEN[1], P. POUTIAINEN[4,5], *J. KURKIPURO[1], L. A. HYDE[3], A. J. NURMI[1], T. A. LANZ[6], A. STEPAN[6], M. A. BAPTISTA[2]
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Abstract: AAV alpha synuclein delivery to rats is used to induce a parkinsonian phenotype and is a common preclinical model of Parkinson's disease. The present work describes parametric studies conducted to evaluate the importance of strain and AAV titer. Because previous research demonstrated that LRRK2 overexpressing G2019S rats are more sensitive to AAV alpha-synuclein treatment relative to WT controls, we decided to test the effect of unilateral infusions of AAV-A53T (1.7 * 1012 vg/mL) on SD and transgenic G2019S-LRRK2 rats. Either 4 or 8 weeks following the infusion, in vivo PET imaging was used to assess DAT levels. The following day, the brains were harvested and TH, DA (and metabolites), Iba-1 immunoreactivity, and alpha-synuclein levels were assessed. In both strains we found significant increase in alpha-synuclein in the infused hemisphere relative to the contralateral hemisphere. Interestingly, unlike previous reports, we found no heightened sensitivity in the G2019S rats when measuring TH. In fact, unlike the SD rats, we did not see a statistical decrease in TH 4 weeks following infusion.

While these data are not consistent with previous findings, more work to evaluate titer levels and AAV treatment regimens are required to compare the two strains.

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Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson's Disease

Title: Behavioral consequences of administration of aav alpha-synuclein to rat

Authors: R. HODGSON[1], *T. PARKKARI[1], T. N. MARTINEZ[2], M. J. FELL[3], L. KOISTINEN[1], T. BRAGGE[1], L. HYDE[3], A. J. NURMI[1], T. A. LANZ[4], A. STEPAN[4], M. A. BAPTISTA[2]
[1]Charles River Discovery, Kuopio, Finland; [2]Michael J Fox Fndn., New York, NY; [3]Merck & Co. Inc., Boston, MA; [4]Pfizer Inc., Cambridge, MA

Abstract: The behavioral consequences of delivery of AAV alpha-synuclein to rat have been modest in most studies, when measured with gross motor assays such as rotarod and locomotor activity in the open field. We have previously reported that the use of a fine kinematic motor analysis to assess animal models of motor dysfunction highlights motor deficits that are not often evident with gross motor endpoints. Here, we have compared fine motor skills of transgenic G2019S-LRRK2, Sprague Dawley and CD rats treated with AAV alpha-synuclein (AAV 2/1 alpha-synuclein: 1.7 x 1012 vg/mL). Four weeks following AAV delivery, fine motor function and gait were assessed using a fine motor kinematic analysis. AAV alpha-synuclein -induced effect on gait was significant in all strains compared to the respective control rats. Several parameters were identified that were affected by the AAV treatment, including hind body posture, the hind limb range of movement (joint angles) as well as hind and forelimb trajectories. These results further demonstrated the sensitivity of the fine kinematic motor analysis assay in the detection of subtle motor deficits in rodents.

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Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Topic: C.03. Parkinson's Disease

Support: AMED

Title: Disease-modifying drugs inhibiting alpha-synuclein aggregation

Authors: *K. FUKUNAGA, Y. YABUKI, K. MATSUO, Y. SHINODA, 980-8578
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Abstract: [Backgrounds] Accumulation and aggregation of alpha-synuclein in dopaminergic neurons is one of pathogenesis of Parkinson's disease (PD), and its formation is partly regulated by long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic acid (AA). Fatty acid binding protein 3 (FABP3, H-FABP) is critical for AA transport and metabolism in the brain. We recently demonstrated that FABP3 is highly expressed in dopaminergic neurons, especially in the substantia nigra pars compacta (SNpc) (J Biol Chem 2014;289:18957). However, the pathophysiological relevance of FABP3 in PD remains unclear. **[Methods]** Wild and FABP3 KO mice were treated with 1-methyl-1,2,3,6-tetrahydropiridine (MPTP) and investigated its neurotoxicity in the SNpc. **[Results]** FABP3 KO mice were resistant to MPTP-induced dopaminergic neurodegeneration and motor deficits. Importantly, MPTP-induced alpha-synuclein accumulation in SNpc was attenuated in FABP3 KO mice compared with that in wild-type mice. In addition, we found that FABP3 overexpression promoted AA-induced alpha-synuclein oligomerization and induced cell death in PC12 cells. Overexpression of FABP3 mutant protein lacking fatty-acid binding region did not promote AA-induced alpha-synuclein oligomerization and cell death. Finally, novel FABP3 ligands ameliorated MPTP-induced alpha-synuclein accumulation/aggregation and rescued dopamine neurons from degeneration in MPTP-treated mice. **[Conclusion]** Taken together, the formation of oligomers of alpha-synuclein is partly regulated by FABP3 through AA binding and metabolism in dopaminergic neurons, contributing to dopaminergic neuronal death seen in PD. We developed FABP ligands as disease-modifying drugs for synucleinopathies in PD. This research is partially supported by the Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and Development, AMED (http://lewybody2016.jp/). The authors declare no conflict of interests.

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Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

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Topic: C.03. Parkinson's Disease

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Title: Rab8a expression mitigates alpha-synuclein toxicity in a rat model of Parkinsonism

Authors: *N. R. MCFARLAND[1], M. S. PARMAR[2], H.-J. PARK[3], D. RYU[2], L. POWELL[4], R. FOELS[4], S. ANAGNOSTIS[4], M. HERRING[5]
[1]Neurol., [2]Neurology/Medicine, [3]Dept. of Aging and Geriatric Res., [4]Univ. of Florida, Gainesville, FL; [5]Broad Inst., Boston, MA

Abstract: Accumulation of α-synuclein (αS) results in endoplasmic reticulum stress, intracellular protein/vesicular trafficking deficits, and cytotoxicity that contribute to Parkinson disease (PD). Increasing evidence suggests that αS in Lewy body disorders interacts with Rab GTPase proteins which have critical functions in intracellular trafficking, transport, and exocytosis. Recently, several Rab GTPases have been shown to be phosphorylated by the lucine-rich repeat kinase 2 (LRRK2) supporting a role in PD. αS-related trafficking deficits, accumulation of intracellular vesicles, and cytotoxicity can be rescued by expression of specific Rab GTPase proteins such as Rab8a. We have recently shown that Rab8a expression potently reduces αS levels and oligomer formation, and rescues Golgi fragmentation, supporting a potential neuroprotective role. Recent data demonstrate that αS interacts with Rab8a in the rodent brain and enhances formation of mature αS aggregates (thought to be protective), reducing cytotoxicity. Together, these data suggest that accrual of αS interferes with the normal function of trafficking proteins and that overexpression of certain Rab GTPases, in particular Rab8a, may restore protein trafficking, homeostasis, and mitigate αS toxicity. To test this hypothesis, we examined the effect viral expression of Rab8a on αS toxicity in a rat model of Parkinsonism. Adult rats were unilaterally injected in the substantia nigra (SN) with recombinant adeno-associated virus (rAAV) serotype 2/8, expressing human αS or empty vector plus or minus Rab8a. All virus were individually tested at several titers for effects and nigrostriatal toxicity, and the concentration for rAAV-Rab8A chosen with lack of independent toxicity. At 8 weeks post injection, rats were sacrificed and brains extracted for histological and biochemical analyses. The results demonstrate robust co-expression of αS and Rab8a in animals that received combined rAAV injection. As expected, expression of αS alone (with empty vector) caused significant (>60%) TH cell loss in SN and accumulation of pathological phosphorylated αS. However, co-expression with Rab8a did not appear to rescue αS-induced TH cell loss in the SN. Despite these findings, viral expression of Rab8a did reduce αS levels in midbrain tissues as

measured by Western blot and partially rescued TH expression in the striatum. These findings correlated with increase/normalization of striatal dopamine and metabolites. While preliminary, these findings provide evidence that targeted viral-mediated Rab8a overexpression can partially rescue αS-mediated nigrostriatal toxicity in a rat model of Parkinsonism.

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Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

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Title: Prolyl oligopeptidase and alpha-synuclein viral vector co-injection increases alpha-synuclein mediated neurotoxicity in prolyl oligopeptidase knock-out animals

Authors: *R. SVARCBAHS, U. JULKU, M. H. SAVOLAINEN, T. T. MYÖHÄNEN
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Abstract: Prolyl oligopeptidase (PREP) is a serine protease able to hydrolyze small proline containing neuropeptides. Recently our research group demonstrated that inhibition of PREP by small molecule inhibitor leads to decreased alpha-synuclein (aSyn) aggregation and restoration of motor behavior in Parkinson's disease animal model. Moreover, animals that lack PREP have altered dopamine transporter phosphorylation and increased dopamine (DA) amount in nigrostriatal tract.
Wild type (wt) and PREP knock-out (PREP-KO) animals received either unilateral aSyn or combined aSyn and PREP (aSyn+PREP) AAV-viral vector microinjection that was followed-up for 13 weeks. PREP-KO animal phenotype was restored to wt mice levels in locomotor activity test 8 weeks after aSyn+PREP injection while aSyn injected PREP-KO animal behavior was statistically different to other animal groups at 8 week time point. Additionally, aSyn+PREP injected animals, both wt and PREP-KO groups, had statistically pronounced drop in the baseline adjusted locomotor activity as opposed to aSyn injected groups.

PREP-KO animals did not show aSyn related toxicity in cylinder test after viral vector injections, nevertheless a significant tyrosine hydroxylase cell loss was observed only in aSyn+PREP injected PREP-KO animals. This observation could be due to higher baseline DA levels in PREP-KO animals that compensate for aSyn mediated unilateral toxicity and offset DAergic cell loss. No-net-flux microdialysis revealed that PREP-KO animals injected with aSyn have decreased ability to re-uptake DA compared to aSyn injected wt animals. Stereology of total aSyn oligomer counts did not show any difference between groups however insoluble aSyn oligomer numbers were decreased in PREP-KO animal group with aSyn+PREP injection as compared to the aSyn injected PREP-KO animals.
Animal data correlates with cell data observations where aSyn aggregation in the presence of PREP increases aSyn nucleation. End point in this experiment is long and could explain comparatively small differences in DA levels and aSyn oligomer number. Our result suggests, that addition of PREP restores PREP-KO animal ability to re-uptake DA at the same time these animals exhibit more pronounced TH positive cell loss that points on PREP role in increasing aSyn mediated toxicity.

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Poster

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Topic: C.03. Parkinson’s Disease

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Georgetown University

Title: Modification of USP13 expression in substantia nigra facilitates clearance of alpha-synuclein and improves motor behavior in wild type and parkin-deficient mice

Authors: *X. LIU, M. HEBRON, M. TANG, D. BOWMAN, C. E. MOUSSA
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Abstract: Alpha-synuclein is a major constituent of Lewy bodies that are the pathological hallmark of Parkinson's disease. We previously showed clearance of alpha-synuclein involves interaction of parkin with the autophagy enzyme Beclin-1. Our preliminary data suggest that the deubiquitinase known as ubiquitin specific protease (USP)-13 modulates parkin activity via de-ubiquitnation and may contribute to alpha-synuclein clearance via autophagy.
In order to elucidate the potential role of USP13 and parkin in alpha-synuclein clearance we

overexpressed lentiviral alpha-synuclein and manipulated USP13 via over-expression or shRNA knockdown in vivo and in vitro in dopaminergic neurons in wild type (WT) and parkin-deficient (PKO) mice.
The levels of alpha-synuclein, soluble and insoluble parkin in nigrostriatal region were measured using ELISA, Western blot and immunohistochemistry methods. Our results show that blocking USP13 expression with shRNA significantly decreased midbrain alpha-synuclein protein levels in both WT and PKO mice. Interestingly, overexpression of USP13 also decreased midbrain α-synuclein protein levels in both WT and PKO mice although to lesser degree. This indicates that clearance of alpha-synuclein is independent or at least partially independent of parkin. Higher levels of soluble parkin protein and lower levels of insoluble parkin protein were noticed in USP13 deletion mice compared to USP13 overexpression in WT mice. This suggests that deletion of USP13 in midbrain improves parkin solubility.
In agreement with above experiments, Rotarod testing show that both USP13 overexpression and deletion significantly improved motor performance from 39% in alpha-synuclein overexpression mice to 89-97% in WT mice and 83-97% in PKO mice, with USP13 deletion being more effective.
Immunohistochemistry studies using mesencephalic neurons from neonatal WT and PKO mice was also consistent with the above findings and showed that both USP13 overexpression and deletion led to significant decrease in the level of alpha-synuclein in both WT and PKO mesencephalon neurons, again, with USP13 deletion being more effective.
In summary, modification of USP13 expression in the SN facilitated the clearance of alpha-synuclein, increased parkin solubility and improved motor performance in a parkin independent manner. It looks that USP13 is a potential therapeutic target for neurodegenerative diseases.

Disclosures: X. Liu: None. **M. Hebron:** None. **M. Tang:** None. **D. Bowman:** None. **C.E. Moussa:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 048.25/V11

Topic: C.03. Parkinson’s Disease

Support: NRF-2015R1A2A1A10052540

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HI14C0093

Title: Anti-aging treatments slow propagation of synucleinopathy by restoring lysosomal function

Authors: *D.-K. KIM[1], H.-S. LIM[2], I. KAWASAKI[3], Y.-H. SHIM[3], N. N. VAIKATH[4], O. EL-AGNAF[5], H.-J. LEE[6], S.-J. LEE[1]
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Abstract: Cell-to-cell transmission of protein aggregates is the underlying mechanism for pathological spreading in age-related neurodegenerative diseases. Under the basis that cell-to-cell transmission of aggregates is associated with the progression of PD, understanding the mechanism of aggregates propagation would be a promising strategy to slow down the progression of disease. Althogh aging is a one of risk factors for progression of disease, the role of aging in spreading of protein aggregates and the mechanism underlying aging-dependent decline of protien homeostasis remain undefined. In this study, we generated *C. elegans* models using bimolecular fluorescence complementation (BiFC) technique for the analysis of aggregate propagation, and these models exhibits many key features of synucleinopathy, including the progressive accumulation of α-synuclein aggregates with age, nerve degeneration, behavioral deficits, and reduced life span. Furthermore, we show that effects of aging-related genetic factors and pharmacological anti-aging treatments on trans-cellualar α-synuclein transmission. Aging promoting genetic variations accelerates the rate of cell-to-cell transmission of α-synuclein aggregates, but pharmacological anti-aging treatments slow aggregate spreading and disease phenotype. Effects of aging and anti-aging agent treatments on propagation of aggregates cause the alteration of protein degradation system. Expression of *hlh-30p::hlh-30*, the master gene of lysosomal biogenesis, in the aging model improves lysosomal function and alleviated intercellular transmission of aggregates in the aging model. These results demonstrate that aging is the major factor of pathological progression of aggregates and anti-aging treatments and enhancer of the lysosomal functions can slow aging-associated disease progression. Thus, these approaches as therapeutic strategies could slowing down the progression of specific protein aggregates in synucleinopathy and other neurodegenerative diseases.

Disclosures: D. Kim: None. **H. Lim:** None. **I. Kawasaki:** None. **Y. Shim:** None. **N.N. Vaikath:** None. **O. El-Agnaf:** None. **H. Lee:** None. **S. Lee:** None.

Poster

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NRF-2015M3A9B4067068

HI16C1012

Title: Olfactory dysfunction and oxidative stress are ameliorated by enriched environment in Parkinson's disease with α-synucleinopathy

Authors: *S. WI[1,2], M. KIM[1,2], J. SEO[1,2], J. LEE[4,5], S.-R. CHO[1,2,3,6]
[1]Dept. and Res. Inst. of Rehabil. Med., [2]Brain Korea 21 PLUS Project for Med. Sci., [3]Rehabil. Inst. of Neuromuscular Dis., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [4]Yonsei Univ. Grad. Sch. of Med., Seoul, Korea, Republic of; [5]Dept. of Physical Med. and Rehabil., Natl. Hlth. Insurance Service Ilsan Hosp., Goyang, Korea, Republic of; [6]Avison Biomed. Res. Ctr., Yonsei Stem Cell Res. Cente, Seoul, Korea, Republic of

Abstract: Parkinson's disease (PD) features non-motor symptoms such as olfactory dysfunction referred as hyposmia, an initial sign of PD's progression. Metabolic dysfunction can contribute to neurodegenerative diseases. Various xenobiotics and endogenous compounds are involved in pathogenesis of PD. Although aerobic exercise induced preservation or improvement olfactory function in PD patients in recent study, exact mechanism is not clear. We aimed to investigate the influence of an enriched environment (EE) on olfactory dysfunction especially via metabolic pathways related with detoxification enzymes. For this, transgenic mice of PD (8 months of age) that overexpress human A53T alpha-synuclein (α-syn) were randomly allocated to EE or standard conditions for two months. Buried food test showed that PD EE group significantly ameliorates olfactory dysfunction compared to PD control group. Results of RT-PCR and qRT-PCR showed that detoxification enzymes--*CYP1A2, PON1, ADH1, UGT2A1, AOH2 and GPX6*--significantly increased in olfactory bulb (OB) of PD control group, but these enzymes normalized in PD EE group. Immunohistochemistry results in OB showed that oxidative stress and nitrated α-syn significantly increased of PD control group, but decreased in PD EE group. In conclusion, we suggest that an EE decreased oxidative stress and nitrated α-syn and normalized detoxification enzymes, resulting in improvement of olfactory dysfunction.

Disclosures: S. Wi: None. **M. Kim:** None. **J. Seo:** None. **J. Lee:** None. **S. Cho:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

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Topic: C.03. Parkinson's Disease

Support: Larry L. Hillblom Fellowship

NIH NS085910

Title: Gut microbiota influence pathophysiology in a mouse model of Parkinson's Disease

Authors: *T. SAMPSON, S. K. MAZMANIAN
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Abstract: The intestinal microbiota influence numerous aspects of host physiology, including central aspects of immunity, metabolism, and more recently neurologic functions. However, functional links connecting gut microbe physiology with neurodegenerative processes remain largely unexplored. Synucleinopathies are diseases characterized by aggregation of the protein α-synuclein (αSyn), often resulting in motor dysfunction as exemplified by Parkinson's disease (PD). Using mice that overexpress wild-type human αSyn, we report herein that gut microbiota are required for characteristic motor deficits and pathology. Alterations to microbial populations in adult animals modulates motor outcomes, suggesting that postnatal signaling between the gut and the brain influences disease. Remarkably, colonization of αSyn-overexpressing mice with microbiota from PD-affected patients exacerbates motor defects compared to microbiota transplants from healthy human donors. Herein, we identify specific microbial taxa and metabolites that are sufficient to potentiate neuroinflammation and motor symptoms in this animal model. Together, these findings reveal that gut bacteria play a role in creating an internal environment conducive for the pathophysiology of neurological illness, and that microbial alterations in humans may represent a risk factor for neurodegenerative disease.

Disclosures: T. Sampson: None. **S.K. Mazmanian:** None.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

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Program#/Poster#: 048.28/V14

Topic: C.03. Parkinson's Disease

Title: Complementary phenotypic characterization of a genetically modified animal model of Parkinson's Disease: Line 61

Authors: S. RAMBOZ[1], K. CIRILLO[1], R. SPRINGER[1], M. MAZZELLA[1], D. HAVAS[1], K. WALKER[1], J. SANCHEZ-PADILA[2], G. TOMBAUGH[2], *A. GHAVAMI[2]
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Abstract: PsychoGenics, Inc has acquired a license for a genetically modified α-synuclein mouse line expressing the human wild-type α-synuclein under the murine Thy-1 promoter (Line 61). This transgenic line has been reported to display pathological features of Parkinson's disease patients including impaired motor and cognitive deficits, α-synuclein aggregates, and

accumulation of phosphorylated α-synuclein in striatum and substantia nigra pars compacta (SNc). For the past year, we have conducted a longitudinal phenotypic profiling of Line 61 using a combination of behavior, in situ analysis of catecholamines, immunohistochemistry, and brain slice electrophysiology. Our data confirm previous published data and demonstrate earlier motor impairment onset. In addition using brain slice electrophysiology, we analyzed spontaneous miniature excitatory postsynaptic currents (mEPSCs) in spiny projection neurons (SPNs) in the dorsal striatum and confirmed a decrease in the frequency but not amplitude of mEPSCs in 6-month old Line 61 mice.

Disclosures: S. Ramboz: A. Employment/Salary (full or part-time):; PsychoGenics. **K. Cirillo:** A. Employment/Salary (full or part-time):; PsychoGenics. **R. Springer:** A. Employment/Salary (full or part-time):; PsychoGenics. **M. Mazzella:** A. Employment/Salary (full or part-time):; PsychoGenics. **D. Havas:** A. Employment/Salary (full or part-time):; PsychoGenics. **K. Walker:** A. Employment/Salary (full or part-time):; PsychoGenics. **J. Sanchez-Padila:** A. Employment/Salary (full or part-time):; PsychoGenics. **G. Tombaugh:** A. Employment/Salary (full or part-time):; PsychoGenics. **A. Ghavami:** A. Employment/Salary (full or part-time):; PsychoGenics.

Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

Location: Halls A-C

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Topic: C.03. Parkinson's Disease

Support: NIH grant AT006868

Title: Synergistic protective effect of sub-therapeutic doses of eicosanoyl-5-hydroxytryptamide and caffeine in α-synuclein transgenic mice

Authors: *R. YAN[1], *R. YAN[1], C. BAUTISTA[1], J. ZHANG[1], E. PARK[1], H.-J. PARK[1], S. OH[1], J. B. STOCK[2], M. M. MOURADIAN[1]
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Abstract: α-Synuclein (α-Syn) aggregates in Lewy-bodies and Lewy-neurites of Parkinson's disease (PD) and Dementia with Lewy Bodies are hyper-phosphorylated, a post-translational modification that promotes the tendency of α-Syn to form fibrils in vitro. In addition, markers of neuroinflammation and oxidative stress are consistent findings in these disorders. Similarly, in the brains of Thy-1 promoter driven α-Syn transgenic mice, pathologic aggregates are hyper-phosphorylated associated with a strong neuroinflammatory reaction and oxidative stress. We previously found that maintaining these mice on a diet supplemented with eicosanoyl-5-hydroxytryptamide (EHT), a natural component of coffee, improved their behavioral phenotype

associated with reduced accumulation of phosphorylated α-Syn aggregates, preserved neuronal integrity, and dampened neuroinflammatory markers, compared to control diet fed α-Syn transgenic mice. Biochemical studies established that EHT enhances the activity of the protein phosphatase 2A (PP2A) isoform that dephosphorylates α-Syn, and that EHT has both anti-oxidant and anti-inflammatory properties. Considering that caffeine also has anti-oxidant and anti-inflammatory properties and, like EHT, has been shown to be protective in the MPTP model of PD, we sought in this study to determine if co-treatment with sub-therapeutic doses of EHT and caffeine could have a protective effect and mitigate the phenotype induced by α-Syn over-expression. α-Syn transgenic mice were given chow containing EHT (at 10% of a behaviorally active dose) and/or water containing caffeine, and their motor and memory performances were assessed on the rotarod, wire hang, nesting behavior and Morris Water Maze. Assessments at 6 months of age showed that, as expected, α-Syn transgenic mice given control diet and water were impaired on all these tests compared to wild-type mice. EHT or caffeine treatment alone had no significant impact on the impaired performance of α-Syn transgenic mice. On the other hand, co-treatment of these mice with the combination of EHT and caffeine significantly prevented their behavioral deterioration measured by all tests. Taken together, these results suggest that the protective effects of EHT and caffeine may converge through common pathways, conceivably involving the regulation of phosphorylation, as well as promoting anti-oxidant and anti-inflammatory responses. The clinical implication of these findings is that ingesting sub-therapeutic small amounts of these compounds in coffee over decades may contribute to the well-recognized reduced risk of developing PD among coffee consumers.

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Poster

048. Alpha-Synuclein Disease Models and Therapeutic Approaches

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Topic: C.03. Parkinson’s Disease

Support: Y20160016

Title: Chronic caffeine treatment exerts cognitive improvement and neuroprotective effects in a mouse model of α-synucleinopathy

Authors: L. YANAN[1], G. YINGZI[1], Z. WU[1], G. WEI[1], C. JIANG-FAN[1,2], *R. XIANGPENG[1]
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Abstract: α-Synucleinopathies, a spectrum of progressive neurodegenerative disorders, most notably Parkinson's disease (PD), are characterized by abnormal accumulation of misfolded α-synuclein (αS)-positive cytoplasmic inclusion, as well as neurodegeneration and cognitive impairments, but the molecular mechanisms underlying αS aggregation and propagation are largely unknown. Using a mouse model of α-synucleinopathy, we recently showed that aberrant adenosine A_{2A} receptor ($A_{2A}R$) signaling contributes to neurodegeneration and cognitive impairments. In this study, we explored the chronic treatment with caffeine (a non-selective antagonist of $A_{2A}R$) could modify neurodegenerative and cognitive phenotypes in the αS transmission mouse model of α-synucleinopathy by injection of preformed A53T αS fibrils into prefrontal cortex region. We showed that chronic caffeine treatment in drinking water (1 g/L) continuously (starting at the time of a-Syn PFF injection and continuing for 60 days) blunted a cascade of pathological events leading to synucleinopathy. Specifically, chronic caffeine treatment attenuated A53T-a-Syn PFF-induced pSer129 α-Syn-rich and p62-positive aggregates, apoptotic neuronal cell death, microglia and astroglia reactivation, NF-kB activation, pronounced neuroinflammation in brain sections compared to water treatment. Furthermore, caffeine treatment also reversed working memory deficits by T-maze-based delay-non-match-to-place test compared to the water treatment. Together with similarly finding from $A_{2A}R$ gene knockout approach, we suggest that chronic caffeine treatment may exert cognitive improvement and neuroprotective effects against αS pathology probably by blocking $A_{2A}Rs$, and thus represent a novel therapeutic strategy for a-synucleiopathy.

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Poster

049. Neuromuscular Diseases

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AMED 17ek0109243h0001

Title: Pathophysiological analysis of skeletal muscles in spinal bulbar muscular atrophy by genome editing of CAG repeats

Authors: *S. TANAKA[1,2], T. ITO[1], A. OTA[3], T. SONE[4], D. SHIMOJO[1,4], S. IMAGAMA[2], Y. HOSOKAWA[3], M. DOYU[1], H. OKANO[4], Y. OKADA[1]
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Abstract: Spinal bulbar muscular atrophy (SBMA) is an adult onset slowly progressive lower motor neuron disease. By the previous analysis using SBMA model mice, mutant androgen receptor (AR) with expanded poly-glutamine tract (polyQ) has been shown to aggregate in spinal motor neurons in testosterone-dependent manner, which has been considered to be the primary pathology of SBMA. However, recent analysis revealed that the pathology in skeletal muscles expressing mutant AR is involved in motor neuron degeneration. Here, we established skeletal muscle disease model of SBMA by the overexpression of mutant AR into human myogenic cell line (Hu5/KD3), or by the expansion of CAG repeats of endogenous AR by CRISPR/Cas9, to reveal pathophysiological changes in skeletal muscles of SBMA.
To examine the pathology of skeletal muscles in SBMA, wild type AR (AR-24Q) or mutant AR (AR-55Q, or -97Q) was transfected into Hu5/KD3 using *piggyBac* vector. After puromycin selection, stably expressing myoblast clones were obtained and differentiated into myotubes in the medium containing 2% horse serum. As a result, abnormal differentiation of myoblasts was observed in CAG-repeat length dependently. To exclude the effects by the overexpression of AR, CAG repeats in endogenous AR was expanded from AR-24Q to AR-55Q or -97Q by CRISPR/Cas9. Consistent with the results of overexpression, CAG repeat-expanded myoblasts exhibited similar abnormal differentiation, though milder than overexpression. These results suggest that the expanded CAG repeat in AR could result in the abnormal differentiation of myoblasts, and may be involved in the skeletal muscle pathology of SBMA. Currently, SBMA disease specific iPSCs, and CAG repeat expansion-corrected SBMA disease specific iPSCs have been established, and are differentiating into skeletal muscles to confirm the phenotypes in SBMA patients'-derived cells. Further analysis would focus on the molecular mechanisms underlying abnormal differentiation of myoblasts, and therapeutic application of genome editing of CAG repeat in skeletal muscles.

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Poster

049. Neuromuscular Diseases

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KOYΛTOYPA/BP-NE/0416/06 to AK

Title: Expanding the gene therapy approach for treating CMT1X inherited neuropathy

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Abstract: *GJB1* gene mutations affecting the gap junction protein connexin32 (Cx32) cause the X-linked Charcot-Marie-Tooth disease (CMT1X), one of the commonest forms of inherited demyelinating peripheral neuropathy). Clinical studies and experimental models indicate that loss of Cx32 function leads to the manifestations of the disease suggesting that gene replacement therapy could offer a therapeutic benefit. In previous studies we have achieved targeted expression of virally delivered Cx32 in Schwann cells following intrathecal injection of lentiviral vectors in the Cx32 knockout (KO) mouse model resulting in morphological and functional improvement. To further examine whether this approach could be effective in patients with CMT1X expressing different mutant forms of Cx32 in Schwann cells, we also treated mutant mice expressing the T55I, R75W and N175D mutations associated with CMT1X on a Cx32 KO background. All three mutants were localized in the perinuclear compartment of myelinating Schwann cells *in vivo* consistent with retention in the ER (T55I) or Golgi (R75W, N175D) with loss of physiological expression in non-compact myelin areas. Following intrathecal gene delivery of the human *GJB1* gene we could detect the virally delivered WT Cx32 correctly localized in the non-compact myelin areas only in T55I/Cx32KO mutant mice, but not in the other two mutants, suggesting dominant effects of the R75W and N175D mutant but not of the T55I mutant on co-expressed WT Cx32. *GJB1* treated T55I/Cx32 KO mice showed improved motor performance, along with lower ratios of abnormally myelinated fibers and reduced numbers of inflammatory cells in all tissues examined compared to mock-treated animals. In contrast, *GJB1* treated R75W and N175D mutant mice showed no significant phenotype improvement. Thus, certain CMT1X mutants may interfere with gene addition therapy for CMT1X. To further clarify the potential for a translatable gene therapy approach we used

repeated intrathecal injections to increase the expression rates, as well as late injections in 6-mo old Cx32 KO mice with already established nerve pathology to examine whether we can achieve similar expression levels of WT Cx32 and reporter gene EGFP as in 2-mo old mice. *Funding: Muscular Dystrophy Association and Charcot-Marie-Tooth Association (Grant MDA 480030 to KAK), Muscular Dystrophy Association (Grant MDA 277250 to KAK), and Cyprus Research Promotion Foundation (ΚΟΥΛΤΟΥΡΑ/BP-NE/0416/06 to AK).*

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Poster

049. Neuromuscular Diseases

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Title: GNB4 mutations lead to dominant intermediate F type of Charcot-Marie-Tooth disease

Authors: *T.-M. CHANG, M.-J. FANN
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Abstract: Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy (HMSN), is the most common inherited neurologic disorder. It was reported that two heterozygous mutations (p.G53D and p.K89E) in the *GNB4* gene are implicated in dominant intermediate F type of Charcot Marie Tooth disease (CMTDIF). *GNB4* encodes G protein beta-4 (GNB4) subunit, which is essential in signaling of G-protein coupled receptors (GPCR). Since GNB4 is the first G-protein component found to be associated with CMT, causality between GNB4-related GPCR signaling and CMTDIF remains elusive. To elucidate the role of GNB4 in CMTDIF, we examined the temporal and spatial expression of *GNB4* during development. It was

found that *GNB4* mRNA is ubiquitously expressed in many tissues, including spinal cord, sciatic nerve and dorsal root ganglion, in postnatal day 7, 35, 240 mice by qPCR. GNB4 conventional knockout (GNB4-KO) and GNB4-G53D-knockin (GNB4-G53D-KI) mice were then generated to detect whether mutant mice exhibit CMT symptoms (motor and sensory impairments, and abnormal nerve conduction velocities (NCV)) through a series of behavioral and NCV tests. As male tends to be more severely affected than female, effects of the gender in behavioral and NCV analyses were also examined. Rotarod, forelimb strength, inverted grid, hot plate, tail flick and vonfrey filament tests were used to measure the motor and sensory functions of transgenic mice every month beginning from two months old. Interestingly, there is no significant difference in all behavioral tests in GNB4-KO mice compared to wildtype, either in male or in female mice. However, homozygous GNB4-G53D-KI male mice fall down sooner than wildtype in the rotarod and inverted grid tests but are normal in forelimb strength test, suggesting that the progression of the disease is in a posterior to anterior manner. In sensory tests, both genders of heterozygous or homozygous GNB4-G53D-KI mice are less sensitive to pain stimuli in tail flick and vonfrey filament tests from two months old. Moreover, G53D mutations of male mice display slower NCV, fewer axonal numbers and damage in myelin sheath in sciatic nerve, which may explain the behavioral results. Taken together, GNB4 mutations are responsible for CMTDIF and CMTDIF is resulted from a gain of function of *GNB4* mutations but not from the loss of the GNB4 normal function.

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Poster

049. Neuromuscular Diseases

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Title: Molecular biomarkers for early diagnostic of cerebral palsy

Authors: *B. ARMISTEAD[1], J. SLAUGHTER[3], M. LENSKI[4], S. OTIENO[2], N. PANETH[5], S. KHOO[1]
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[4]Epidemiology and Biostatistics, [5]Pediatrics and Human Hlth., Michigan State Univ., East Lansing, MI

Abstract: Cerebral Palsy (CP) describes a group of complex neurological disorders that cause life-long motor impairments. Besides motor dysfunction, nearly all patients with CP suffer from comorbidities, which can include seizures and visual, speech, cognitive, and learning disabilities. The diagnosis of CP cannot be securely made until motor development is sufficiently advanced to reliably assess deficits, usually around the age of 2. It would be valuable to have early indicators of risk for CP beyond those collected clinically, such as preterm birth and labor difficulties. In addition, genes preferentially expressed at birth in children who later develop CP may indicate pathways that might suggest possibilities for prevention. Previously, we used microarray technology to identify several differentially expressed genes from four hypothesized pathways–inflammatory, hypoxic, coagulative, and thyroidal–from archived neonatal blood spots (NBS) of 53 CP children and 53 age-, gender-, and gestation age-matched healthy controls (HC). Three-3mm punches were taken from each bloodspot and homogenized to extract messenger RNA (mRNA). mRNA was amplified and converted to complementary DNA (cDNA) before hybridization onto Agilent whole human genome gene expression microarrays. Here, we applied quantitative real-time PCR (qRT-PCR) on NBS of 22 pre-term CP infants and 23 gestational age- and birth weight-matched HC to evaluate gene expression of two differentially expressed genes from the inflammatory pathway: S100 calcium binding protein A9 (*S100A9*) and ectonucleoside triphosphate diphosphohydrolase-1 (*ENTPD1*). The Markov Chain Monte Carlo simulation was used to normalize qRT-PCR data and an ANCOVA test was applied to test for statistical significance, while controlling for gender, gestation age, and birth weight. We obtained P-values of 0.3192 and 0.4327 for *S100A9* and *ENTPD1,* respectively. Although there was no statistically significant difference in gene expression between CP and HC, an overall up-regulated trend for both *S100A9* and *ENTPD1* in CP compared with HC was observed, which was consistent with our microarray findings. Our future directions are to investigate the expression of *S100A9* and *ENTPD1* with a larger sample size and also test additional target inflammatory genes, namely tumor necrosis factor- (*TNF*-) and tyrosine hydroxylase (*TH*). Furthermore, we will compare the gene expression in term and preterm CP samples to better understand CP pathways in these different risk groups. Our results will help determine a set of genes to serve as early diagnostic biomarkers for CP.

Disclosures: B. Armistead: None. **J. Slaughter:** None. **M. Lenski:** None. **S. Otieno:** None. **N. Paneth:** None. **S. Khoo:** None.

Poster

049. Neuromuscular Diseases

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 049.05/V21

Topic: C.05. Neuromuscular Diseases

Support: NIH Grant R01 NS038526

NIH Grant P30 NS045758

Title: Charcot-Marie-Tooth disease type 2E mutant neurofilament subunit proteins assemble into neurofilaments

Authors: *E. STONE[1], A. UCHIDA[2], A. BROWN[2]
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Abstract: Charcot-Marie-Tooth (CMT) is a slow, progressive peripheral neurodegenerative disease inherited with autosomal dominance. The CMT subtype “2E” defines the disease as an axonopathy arising from mutations in the gene that encodes for the low molecular weight neurofilament subunit protein (NFL). NFL is one of five subunits that comprise neurofilaments, which are neuron-specific cytoskeletal polymers that fulfill a structural role in axons. Some previous studies in cell culture have shown that the mutant proteins make amorphous aggregates rather than distinct polymers and have therefore concluded that pathology is caused by a dominant negative effect of the mutant proteins on neurofilament assembly. However, electron micrographs of patient nerve biopsies depict swollen axons full of neurofilament polymers. In order to reconcile these apparently conflicting observations, we have reexamined the polymerization capability of CMT2E mutant NFL protein. We have done this by co-expressing CMT2E mutant NFL with wild type neurofilament protein subunits in neurons and in a cell line that lacks endogenous intermediate filament proteins, and then visualizing the proteins by fluorescence microscopy. We found that several of the CMT2E NFL mutant proteins co-assemble freely into filaments with one other wild type subunit, and that others could also co-assemble if additional subunits were also present. These data highlight the importance of subunit composition in evaluating the assembly of neurofilament proteins, and they question the prevailing notion that neurofilament assembly is defective in CMT2E disease. We propose that CMT2E disease is not caused by a disruption of neurofilament assembly, but rather by other mechanisms such as changes in neurofilament polymer transport or polymer or subunit interactions.

Disclosures: E. Stone: None. **A. Uchida:** None. **A. Brown:** None.

Poster

049. Neuromuscular Diseases

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 049.06/V22

Topic: C.05. Neuromuscular Diseases

Support: NIH RO1NS049117

MDA 134412

Title: Pathogenic effects of the agrin V1727F mutation are neural agrin specific and decrease its expression and affinity for LRP4

Authors: J. RUDELL[1], R. MASELLI[2], *M. J. FERNS[3]
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Abstract: Agrin is a large, alternatively spliced proteoglycan whose isoforms differ in their tissue distribution and function. Agrin containing z site inserts (z+) is neural-specific and regulates the formation of the neuromuscular junction (NMJ), while z- agrin, which lacks the z site inserts, is more ubiquitous and has many proposed functions in various tissue types. Previously we identified a missense mutation (V1727F) in the second laminin G-like (LG2) domain of agrin that causes severe congenital myasthenic syndrome. Here, we investigate how the V1727F mutation impairs agrin expression and its ability to activate the MuSK receptor at the NMJ, resulting in impaired synaptic transmission. To assay expression, we transfected HEK cells with wild type (WT) or V1727F z+ and z- agrin then compared the levels of agrin in the cellular fraction and conditioned media by immunoblotting. All agrin variants were detected at similar levels in the cellular fraction. However, levels in the conditioned media were ~80% lower for V1727F compared to WT z+ agrin, but equivalent for V1727F and WT z- agrin. Thus, the V1727F mutation impairs the secretion and functional levels of only neural z+ agrin. Next, to define the basis for impaired receptor signaling, we compared binding of WT and V1727F z+ agrin and z- agrin (5 nM concentration) to the LRP4 co-receptor, which mediates agrin's activation of MuSK. For this, we expressed full-length LRP4 in HEK cells and measured binding of the agrin variants using an On-cell Western assay. We found that V1727F z+ agrin bound LRP4 at levels 75% lower than WT z+ agrin, and at levels similar to WT z- agrin. Surprisingly, agrin binding to LRP4 was followed by pronounced internalization from the cell surface, with agrin accumulating in intracellular puncta that partially colocalized with LRP4. Together, our findings demonstrate that the V1727F mutation inhibits neural (z+) agrin secretion and its ability to bind LRP4. Both of these defects likely contribute to the pathogenesis of the disease. Remarkably, the functional deficits caused by the mutation are confined to z+ agrin, and suggest that the LG2 domain is critical for its correct conformation and for high affinity binding to LRP4. The z+ isoform-specific effects likely also account for the selective NMJ defects observed in the patient, as z- agrin function in other tissues is probably not significantly impaired.

Disclosures: J. Rudell: None. **R. Maselli:** None. **M.J. Ferns:** None.

Poster

049. Neuromuscular Diseases

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 049.07/V23

Topic: C.05. Neuromuscular Diseases

Support: University of Sydney Bridging Support Grants 2015-17

Title: Overexpression of MuSK protects dystrophic mdx mouse muscles against stretch-induced loss of force

Authors: J. BAN, S. TRAJANOVSKA, *W. D. PHILLIPS
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Abstract: Mdx mice serve as the most common mouse model for Duchenne muscular dystrophy (DMD). Their muscles lack dystrophin and are more prone to stretch-induced injury than wild-type muscles. Mdx muscles are also reported to express less Muscle Specific Kinase (MuSK) than wild-type muscles. While MuSK is vital for stabilizing the mammalian neuromuscular junction (NMJ) its broader role in muscle physiology remains uncertain. We used adeno-associated viral vector (AAV) to overexpress MuSK (fused to GFP) in mice. The tibialis anterior muscles of 8-week old male mdx mice were injected with AAV-MuSK-GFP. The contralateral muscle received empty AAV vector. Three weeks later, MuSK-GFP was strongly expressed in the postsynaptic membrane of the NMJ and at lower densities in the extrasynaptic sarcolemma. The mice were anaesthetized with isoflurane and maximum tetanic force was recorded in response to direct muscle stimulation. After a series of four eccentric (stretch) contractions, mdx muscles retained only 73 ± 2% of their original (pre-stretch) maximum isometric force. In contrast mdx muscles expressing MuSK-GFP retained 84 ± 1% of their original force after identical ECs ($p<0.01$). Rapsyn, an established downstream effector of MuSK signaling, conferred similar protection to mdx muscles. When contraction was elicited instead via the nerve, muscles expressing MuSK-GFP showed decay of force during each 400msec tetanus suggesting fatigue of neuromuscular transmission. These results indicate that enhanced MuSK-rapsyn signaling can protect dystrophin-deficient muscle fibers from acute eccentric stretch-induced loss of force. They also suggest that MuSK may play some role in negatively regulating the capacity for prolonged (tetanic) neuromuscular transmission.

Disclosures: J. Ban: None. **S. Trajanovska:** None. **W.D. Phillips:** None.

Poster

049. Neuromuscular Diseases

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 049.08/V24

Topic: C.05. Neuromuscular Diseases

Support: SURE (Summer Undergraduate Research Experience) Award Program

Title: Identifying the metal that activates the prenyltransferase that catalyzes formation of geranyl diphosphate in the diatom pseudo-nitzschia multiseries

Authors: *H. TRAN
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Abstract: Domoic acid (DA) is a neurotoxin synthesized by marine diatoms of the genus Pseudo-nitzschia which causes amnesiac shellfish poisoning in humans and death of marine wildlife. DA mimics the neurotransmitter glutamate and overstimulates glutamate receptors in the nervous system that leads to uncontrolled influx of calcium and ultimately causes degeneration of nerve cells. Geranyl diphosphate (GPP), a key intermediate in domoic acid biosynthesis, is formed from the “head-to-tail” condensation of isopentenyl diphosphate and dimethylallyl diphosphate in a reaction catalyzed by a member of the prenyltransferase family of enzymes. These prenyltransferases can generate different chain-length products, including geranyl diphosphate (C10), farnesyl diphosphate (FPP, C15), and geranylgeranyl diphosphate (GGPP, C20), all of which are precursors to terpenoid natural products. Prenyltransferases require a divalent metal cation for activity. Previous work has shown that a single prenyltransferase can generate multiple products (GPP, FPP, and GGPP), and that the product distribution will vary depending on the species of divalent cation used to support the reaction (Mg^{2+}, Mn^{2+}, or Co^{2+}). Here, we measured the levels of Mg^{2+}, Mn^{2+}, and Co^{2+} in Pseudo-nitzschia cells to determine which ion is most likely to support GPP formation. Three samples of Pseudo-nitzschia multiseries cultured in sea water were harvested by centrifugation. Samples were digested with HNO_3 before analysis using atomic absorption spectroscopy. The average concentration of Mg^{2+} present, per cell and per µm3, is over 100- fold higher than the concentrations of Mn^{2+} and Co^{2+}. This is consistent with results from studies in other systems, suggesting that Mg^{2+} is the main cofactor that activates the prenyltransferase that generates GPP for domoic acid biosynthesis in Pseudo-nitzschia.

Disclosures: H. Tran: None.

Poster

049. Neuromuscular Diseases

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 049.09/V25

Topic: C.05. Neuromuscular Diseases

Title: Effects of aging on the jaw-opening produced by cholinergic motor neurons concerning feeding behaviors of *Aplysia* kurodai

Authors: *T. NAGAHAMA, A. KASHIMA
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Abstract: In the wild animals of *Aplysia kurodai*, we previously reported that the amount of food intake significantly decreased with age and this may result in weight loss of old animals. Such age-dependent behavioral changes may be caused by full or partial disorders of the taste sensory system, the central nervous system, and the feeding motor system. In the preceding experiments, effects of aging on the synaptic function in the feeding neural circuit were explored and the synaptic response in the jaw-closing motor neurons (JCs) induced by the cholinergic multi-action neurons (MAs) significantly decreased with age. Because reduction of this synaptic response by the dopaminergic modulatory neuron may contribute to generation of the patterned firing of the motor neurons for food rejection as shown in our earlier studies for food preference behavior, the dysfunction of this cholinergic synapse may partly contribute to the decline of the food intake with aging. In the present experiments, we focused on the effects of aging on the jaw-opening movements produced by the cholinergic jaw-opening motor neurons (JOs) in the feeding motor systems. The collected animals were classified into mature and old animals by using our newly found index of “old age” as reported previously. When we explored the relationship between the JO spike number evoked by 1 s depolarizing current pulse and the induced muscle tension, the slope of the increase in the tension intensity with increasing spike number was significantly lower in old animals than mature animals. And the threshold spike number initiating the muscle tension was significantly larger in old animals than mature animals. These results suggest that the movements of the jaw-opening muscle (JOM) may decline with age and the dysfunction of the jaw opening may largely contribute to the age-dependent decline of the food intake. In addition, we extracellularly explored the size of the excitatory junction potentials (EJPs) in the JOM induced by the JO firing in mature and old animals to know the origin of the tension decrease with age. The size of the first EJP induced by the JO firing was significantly smaller in old animals than mature animals. These results suggest that the cholinergic response in the neuromuscular synapse may decline with age in a similar way to the cholinergic synaptic response in the central nervous system.

Disclosures: T. Nagahama: None. **A. Kashima:** None.

Poster

049. Neuromuscular Diseases

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 049.10/V26

Topic: C.05. Neuromuscular Diseases

Title: CNS targeted AAV mediated gene therapy alleviates pathological and clinical progression of Krabbe disease in twitcher mice

Authors: *C. W. LEE[1], A. R. HERDT[1], D. W. DICKSON[2], T. E. GOLDE[3], C. B. ECKMAN[1]
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Abstract: Globoid Cell Leukodystrophy (GLD), or known as Krabbe disease, is a monogenetic, autosomal recessive, devastating neurological disorder. Inheritance of loss-of-function mutations in the galactocerebrosidase (GALC) gene leads to toxic accumulation of its substrate psychosine in myelinated brain regions, which is central to the pathophysiology of the disease. To achieve global transduction of *GALC* gene in the central nervous system (CNS), the murine *GALC* expressing vector, packaged in adeno-associated virus serotype 1 (AAV1) was administrated through intracerebroventricular (icv) route at neonatal age in the Twitcher mice - a naturally occurring, authentic mouse model of GLD. Global expression of GALC protein was achieved in various regions of CNS with the highest levels in cortex, hippocampus, thalamus and midbrain. Moderate expression levels were found in midbrain, cerebellum, brain stem and spinal cord. Pathological features such as accumulation of globoid cells and astrogliosis were virtually absent in the regions with high GALC levels, and reduced significantly in the regions expressing lower levels of GALC, such as the cerebellum, brain stem and spinal cord. Biochemically, psychosine levels in the fore- and midbrain regions were completely reversed to wildtype levels. About 80% psychosine clearance was achieved in the hindbrain region in end-stage treated mice compared to end-stage untreated control. As a result of the pathological improvement, the lifespans of the Twitcher mice were extended from an average of 42 days in untreated mice to an average of 84 days in treated mice. One treated mouse lived until 126 days. Our data support that AAV-mediated *GALC* gene therapy in CNS is efficacious in halting disease progression and improving survival of patients through alleviating GLD-specific pathologies.

Disclosures: C.W. Lee: None. **A.R. Herdt:** None. **D.W. Dickson:** None. **T.E. Golde:** None. **C.B. Eckman:** None.

Poster

049. Neuromuscular Diseases

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 049.11/W1

Topic: C.05. Neuromuscular Diseases

Support: New Jersey Commission on Spinal Cord Research

Title: Blood brain barrier dysfunction following inactivation of Hh signaling in adult mouse spinal cord astrocytes

Authors: *H. WANG[1], M. RALLO[1], M. MATISE[2]
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Abstract: Blood-brain/spinal cord barrier (BBB) disruption is recognized as a critical early event in the etiology of many diseases affecting the CNS and spinal cord (SC), including Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS). BBB permeability is regulated by several distinct cell types comprising the "neurovascular unit" (NVU), including blood vessel endothelial cells (ECs), pericytes, and astrocytes.
Due to its well-established role in stem cell maintenance and proliferation, Hedgehog (Hh) signaling has been the focus of a number of studies that seek to determine whether this pathway plays a role in the response to CNS lesions, injuries, or disease. Sonic Hedgehog (Shh) signaling has been implicated in maintaining the BBB under normal conditions, and is also up-regulated in the CNS following various types of injuries and diseases. However, a number of important issues remain unclear about the complex role of Shh in BBB maintenance and injury response/repair, including the definitive identification and characterization of the responsive cell subpopulation/s involved.
We have discovered that the Shh pathway is active in a specific subset of mature astrocytes in the gray matter (GM) of the adult mammalian SC, as revealed by their expression of Gli1, a Shh target gene and pathway mediator, that are in close association with blood vessels. These data indicate that Gli1+ (expressing) astrocytes exhibit a molecular genetic identity distinct from all other glial cell populations in this tissue, raising the possibility that they also have a unique function. Consistent with this, conditional genetic inactivation of the Hh pathway in these cells in adults results in rapid breakdown of the BBB in both the brain and spinal cord, revealed by extravasation of systemically-injected tracers and other vascular proteins, as well as immunohistochemistry. Interestingly, the BBB is restored several days following pathway inactivation, via both Hh-dependent and –independent mechanisms. These findings reveal a critical role for Hh signaling in a subset of GM astrocytes in the maintenance of the BBB under

normal conditions. Experiments are currently underway to evaluate the role of the pathway in mediating the response following demyelinating injuries to the CNS.

Disclosures: H. Wang: None. **M. Rallo:** None. **M. Matise:** None.

Poster

049. Neuromuscular Diseases

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Program#/Poster#: 049.12/W2

Topic: C.05. Neuromuscular Diseases

Support: NIH Grant NS054154

NIH Grant OD020351

Title: Peripheral neuropathy-associated mutations in tRNA synthetase genes are pathogenic in mouse models

Authors: I. BAGASRAWALA[1], M. G. STUM[1], K. H. MORELLI[2,3], E. L. SPAULDING[2,3], K. L. SEBURN[1], *R. W. BURGESS[1,2]
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Abstract: Charcot–Marie–Tooth disease (CMT) is a heterogeneous group of rare inherited peripheral neuropathies affecting ~1 in 2500 people worldwide. Many CMTs exhibit an autosomal dominant mode of inheritance. CMT can be demyelinating (type 1), axonal (type 2), or dominant intermediate (DI), having both axonal and demyelinating features. Dominant mutations in the *GARS* gene, encoding the enzyme glycyl-tRNA synthetase, cause CMT type 2D (CMT2D). One variant, *GARS*^{S635L}, has been reported in a few cases of CMT2D, but its disease association and pathogenicity are ambiguous. Similarly, mutations in the *YARS* gene, which encodes tyrosyl tRNA synthetase, cause DI-CMTC, and the *YARS*^{E196K} variant is disease-associated. Since the molecular mechanisms through which mutations in aminoacyl-tRNA synthetases lead to peripheral neuropathy currently are unknown, no therapy has proven to be effective to date. To gain insight into the pathophysiology of CMT, we developed CMT2D *Gars*^{S625L} (the equivalent of S635L in humans) and DI-CMTC *Yars*^{E196K} mouse models on the C57BL/6J backgrounds. These mouse models enable us to test the pathogenicity of the *Gars*^{S625L} allele, and provide the first mouse model of DI-CMTC. We are now testing whether these mice replicate the disease phenotype in order to study the time of disease onset, disease mechanism, inheritance pattern, and to perform preclinical studies. Preliminary results with grip strength, nerve conduction velocities, and motor and sensory nerve histology indicate a dominant neuropathy in both the *Gars*^{S625L} and the *Yars*^{E196K} mutations, appearing at 8 months and 7

months of age, respectively. Therefore, the *Gars*^{S625L} and *Yars*^{E196K} mutations are pathogenic in mice, causing a late-onset peripheral neuropathy. Additional studies in these mouse models will provide a better understanding of tRNA synthetase mutations and peripheral axon degeneration.

Disclosures: I. Bagasrawala: None. **M.G. Stum:** None. **K.H. Morelli:** None. **E.L. Spaulding:** None. **K.L. Seburn:** None. **R.W. Burgess:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.01/W3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 5T32GM007288-43

Title: Sensory impairment and related neuropathology in a mouse model of Christianson syndrome: Evidence of endosomal-lysosomal disruption

Authors: M. KERNER-ROSSI[1], K. DOBRENIS[2], M. GULINELLO[3], *S. U. WALKLEY[4]
[2]Neurosci., [3]Behavioral Core, Dept. of Neurosci., [1]Albert Einstein Col. of Med., Bronx, NY; [4]Albert Einstein Col. Med., Bronx, NY

Abstract: Christianson syndrome (CS) is a recently described X-linked neurological disorder with clinical features that include severe intellectual disability (ID), epilepsy, postnatal microcephaly, regressions in cognitive and motor skills, and progressive ataxia. Prior to discovery of the genetic basis, many patients were mis-diagnosed with Angelman syndrome, due to phenotypic similarity, especially a characteristic “happy demeanor.” In 2008 it was shown that mutations in *SLC9A6* are responsible for CS. Although currently considered an ultra-rare disorder, genomic studies suggest that *SLC9A6* mutations may be among the most common causes of X-linked ID.
SLC9A6 encodes the endosomal sodium-hydrogen exchanger, NHE6, thought to regulate luminal pH of early and recycling endosomes. Previously, our lab showed that *Slc9a6* knockout (KO) mice replicate several of the phenotypic features of CS at the behavioral level (e.g., progressive motor deficit and impaired visuospatial memory). Importantly, we identified pathology highly similar to that occurring in several primary lysosomal diseases, such as late endosomal/lysosomal accumulation of GM2 ganglioside in select brain regions (including basolateral amygdala and hippocampus), as well as a progressive, patterned degeneration of cerebellar Purkinje neurons with axonal spheroids. These findings suggest that, despite the endosomal location of NHE6, the clinical features of CS may be due in part to broader disruptions to the endosomal-lysosomal system.
Parental reports of sensory disturbances in their affected (male) children, such as an apparent

insensitivity to pain, led us to explore sensory function in *Slc9a6* KO mice. Using multiple behavioral analyses, we demonstrate that male (i.e. hemizygous) KO mice have reduced responses to thermal and pressure stimuli (Hargreaves and Von Frey assays, respectively), as compared with wild type (WT) littermates. Post-mortem immunohistochemical analysis of spinal cord revealed GM2 ganglioside accumulation in dorsal horn neurons of KO but not WT mice. Intriguingly, GM2 was most abundant within neurons of lamina I of the dorsal horn, and found at all spinal levels. The spinal cords of aged KO mice also exhibited marked astrogliosis and elevated CD68-positive microglia throughout the entire gray matter, although spinal reflexes were intact and comparable to WT. Given the selective sensory impairments as well as the localized accumulation of GM2 within lamina I (a major relay site in the processing of noxious stimuli), we hypothesize that the sensory disturbances occurring within CS are related to lysosomal dysfunction in neurons within the nociceptive pathway.

Disclosures: M. Kerner-Rossi: None. **K. Dobrenis:** None. **M. Gulinello:** None. **S.U. Walkley:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.02/W4

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: SFB CRC-128 B06

SFB CRC-128 B05

Title: Neuronal spatiotemporal alterations in the cuprizone model of general de- and remyelination

Authors: *M. CERINA[1], V. NARAYANAN[1], A. DELANK[1], P. MEUTH[1], S. GRAEBENITZ[2], K. GOEBEL[1], A. HERRMANN[1], S. ALBRECHT[3], T. DALDRUP[2], T. SEIDENBECHER[2], A. GORJI[4], H. WIENDL[1], C. KLEINSCHNITZ[5], E.-J. SPECKMANN[2], H.-C. PAPE[2], S. MEUTH[1], T. BUDDE[2]
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Abstract: The neocortex in both humans and rodents is characterized by a well-conserved structure and high-level of organization. The presence of layering, clustering of neurons and glia, and the segregation of the different white matter bundles are what render these structures unique

and complex. Alterations in cortical layering, cellular organization and functionality are associated with the occurrence of diseases such as multiple sclerosis (MS). Recently, the appearance of altered, unorganized and damaged thalamocortical structures was shown to be associated with demyelination and functional cognitive and locomotor deficits both in humans and animals. Therefore, we aimed to assess network properties of the primary auditory cortex in mice by using the cuprizone model of general de- and remyeliantion. Voltage sensitive dye (VSD) imaging and extracellular field potential recordings showed changes in the spatiotemporal propagation of the stimulus as well as in response latency, which persisted during remyelination suggesting a profound effect exerted on neuronal network level. Altered propagation patterns of incoming stimuli was reflected in vivo as permanent loss of auditory discrimination abilities in freely behaving animals. Therefore, in order to assess the extent of neuronal contribution to such deficits, we tested the cytoprotective effects of different compounds used in MS therapy. In our study, therapeutic treatment with some of the compounds during remyelination, both an early and late stage of this process, ameliorated cortical functionality both in vitro and in vivo. Taken together our results support the neuronal involvement in regulating spatio temporal cortical pattern following myelin gain and loss and indicates a therapeutic window of intervention.

Disclosures: **M. Cerina:** None. **V. Narayanan:** None. **A. Delank:** None. **P. Meuth:** None. **S. Graebenitz:** None. **K. Goebel:** None. **A. Herrmann:** None. **S. Albrecht:** None. **T. Daldrup:** None. **T. Seidenbecher:** None. **A. Gorji:** None. **H. Wiendl:** None. **C. Kleinschnitz:** None. **E. Speckmann:** None. **H. Pape:** None. **S. Meuth:** None. **T. Budde:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.03/W5

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NMSS RG5351-A-10

NIH 1R21NS093134-01A1

Title: The effect of anti-Axl and anti-Mertk antibodies on the CNS during experimental autoimmune encephalomyelitis (EAE)

Authors: *J. C. DUBOIS[1], ***J. C. DUBOIS**[1], A. RAY[2], B. SHAFIT-ZAGARDO[3]
[1]Pathology, [2]Albert Einstein Col. of Med., Bronx, NY; [3]Albert Einstein Col. Med., Bronx, NY

Abstract: Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) characterized by inflammation, loss of oligodendrocytes, demyelination, and damaged axons. The Tyro3, Axl and Mertk (TAM) family of receptor tyrosine kinases are important for

innate immune responses and CNS homeostasis. Their ligand Growth Arrest-Specific Protein 6 (Gas6) activates all three receptors, while ProteinS1 (ProS1) can only activate Tyro3 and Mertk, making Gas6 the sole ligand for Axl. Previous work from our laboratory has determined that during myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE), *Mertk* and *Axl* mRNA expression are significantly elevated at 4 and 8 days following the onset of EAE symptoms respectively, and Gas6 administered directly to the brain is neuroprotective. However, no major benefit was observed when Gas6 was administered to the brains of $Axl^{-/-}$ mice, suggesting that Gas6 activation of Axl is necessary for the protective effect observed during MOG-induced EAE. Gas6 has a short half-life. Therefore, we sought to determine whether intraperitoneal administration of an activating anti-Axl antibody or anti-Mertk antibody could effectively reduce the clinical course of EAE, thereby reducing inflammation and neurodegeneration. We injected four groups of C57BL6J mice with an activating anti-Axl antibody, an anti-Mertk antibody, IgG isotype control or PBS prior to mice presenting with clinical scores, and during the acute phase of the disease. When injected with anti-Axl prior to the onset of clinical symptoms, there was a decrease in the clinical scores of male mice. H&E analysis of the spinal cords showed a reduction in the number of infiltrating inflammatory cells when compared to mice treated with IgG isotype control. When injected with anti-Mertk antibody prior to the onset of clinical symptoms, there was no difference in clinical scores compared to IgG control treated mice. Ongoing studies are further characterizing the spinal cords of these groups of mice. Hence, our data suggests that the beneficial effect of Gas6/Axl signaling observed in mice administered Gas6 directly to the CNS, can be preserved by injecting mice with an activating anti-Axl antibody, but not the anti-Mertk antibody.

Disclosures: J.C. DuBois: None. **A. Ray:** None. **B. Shafit-Zagardo:** None.

Poster

050. Neuroinflammation

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Program#/Poster#: 050.04/W6

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: RO1 MH098554 from NIMH

Title: Protein and mRNA expression of membrane-bound cytokine receptors in the teenage suicide brain

Authors: *X. REN
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Abstract: Abnormalities of the immune function in depression and suicide are based in part on the observation of increased levels of proinflammatory cytokines in the serum and in postmortem

brain of depressed and suicidal patients. Several studies suggest dysregulation of the immune system in suicide as increased microgliosis has been reported in postmortem brain of suicide subjects and increased levels of proinflammatory cytokines in the CSF of suicidal patients. This observed abnormality of cytokines in suicide may be related to altered innate immune receptors known as cytokine receptors such as TNF receptors, IL-1 receptors and IL-6 receptors. In the previous studies we reported a significant increase in the protein and mRNA levels of cytokines such as TNF-α, IL-1 and IL-6. To further examine the role of cytokine receptors in suicide we have now studied the protein and mRNA expression of TNFR1, TNFR2, IL-1R1, IL-1R2 IL-6Ra and Gp130 in teenage suicide subjects.
We determined the protein and mRNA expression of TNFR1, TNFR2, IL- R1, IL-1R2 IL-6Ra and Gp130 in the PFC of 17 teenage suicide victim and 17 normal control subjects. The postmortem brain tissues were obtained from the Maryland Brain Collection and the psychological autopsies were performed for the diagnosis of the subjects using DSM-IV-SCID. Protein and mRNA expression were determined using Western blot technique and qPCR, respectively.
When we compared the protein and mRNA expression of Gp130, we found that the expression of Gp130 protein and mRNA were significantly decreased in teenage suicide victims compared with normal control subjects, while there was no difference in the protein and mRNA expression of TNFR1, TNFR2, IL-1R1, IL-1R2 and IL-6Ra in teenage suicide victims compared with normal control subjects.
These results suggest that decreased mRNA and protein of Gp130 may be in part related to the abnormalities of proinflammatory cytokines in the brain of suicide victims and that abnormalities of innate immunity are associated with suicide.
(Support contributed by a grant RO1 MH098554 from NIMH)

Disclosures: X. Ren: None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.05/W7

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: PICT 2013

AGENCIA NACIONAL DE PROMOCION CIENTIFICA Y TECNOLOGICA

Title: Effect of the cytokine interleukin 6 on acid sensing ion channel (ASIC1) distribution in hippocampal neurons

Authors: *C. WEISSMANN, L. C. SALINAS, C. GONZÁLEZ INCHAUSPE, P. PERISSINOTTI, O. D. UCHITEL
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Abstract: Neuroinflammation has long been analyzed as a contributor to neurodegenerative processes. The inflammation hypothesis proposes that chronic inflammatory response is a crucial factor in the onset and progression of neurodegeneration.Cytokines are essential modulators of the immune response; and Interleukin 6 (IL-6) is one of the main neuroinflammatory cytokines in the central nervous system (CNS). Both glial and neuronal cells express IL-6 and IL-6R (receptor) in the brain. CNS IL-6 is upregulated when neuroinflammation occurs, and IL-6 levels are increased in sera of Parkinson's, Huntington's as well as in animal models of these diseases. In addition, inflammation determines changes in metabolic activity and can result in acidosis. Changes in regional pH levels in the brain have been observed in a number of neurological and neurodegenerative disorders. ASIC (Acid sensing Ion) channels are sodium channels activated by tissue acidosis and thus become active in many pathological conditions. ASIC1 is the most abundant ASIC subunit in the mammalian central nervous system. Physiologically, its activation is related to synaptic plasticity, learning and memory. ASIC1 channels in particular permeate not only sodium but slightly calcium ions, and so can contribute to intracellular calcium levels and neuronal injury in pathological conditions. In fact, ASIC1 channels have been lately implicated in several neurological diseases, as blocking this channel with ASIC1 toxin improves models of cerebral ischemia, Parkinson´s disease, Huntington´s and ALS. Therefore, we decided to analyze the role of IL-6 on ASIC1 channels.
We studied dissociated mouse hippocampal cultures after 8-12 DIV (days in vitro). We incubated the cultures with IL-6 (10 ng/ml 30 minutes) and did immunocytochemistry of the samples to detect ASIC1. In parallel we studied the ASIC currents elicited by applying a puf of saline at pH 6.1 under whole cell patch-clamp conditions. Our preliminary results show that IL-6 determines the redistribution of a cytosolic pool of ASIC1 channels to the membrane of the neurons, which correlates with an increase in ASIC1 currents amplitude.These results point at a mechanism by which neuroinflammation could contribute to neurodegeneration; and ASIC1 as a potential target to aim at in these conditions.

Disclosures: C. Weissmann: None. **L.C. Salinas:** None. **C. González Inchauspe:** None. **P. Perissinotti:** None. **O.D. Uchitel:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.06/W8

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: 7,8-Dihydroxyflavone decreases the inflammation and clinical severity of optic neuritis in experimental autoimmune encephalomyelitis

Authors: M. I. ARVAS[1], P. R. GUDA[2], *T. K. MAKAR[2,3,4], D. TRISLER[2,3,4], C. BEVER, Jr[3,4]
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Abstract: Multiple sclerosis (MS), an inflammatory autoimmune disease, is characterized by inflammation, demyelination, axonal injury and gliosis and diffuse axonal degeneration in the CNS. Optic neuritis (ON), a common feature of MS, characterized by inflammation of the optic nerve, may affect blood perfusion of the ocular vessels and possibly damage visual acuity. Studies on MS find significant axonal damage, thinning of the retinal nerve fiber layer and a decline of retinal ganglion cells together with a loss of vision. Most patients recover from this vision loss after several weeks. But in 40% of these patients vision loss remains permanent. Experimental autoimmune encephalomyelitis (EAE) induced by inoculation of myelin oligodendrocyte glycoprotein (MOG) peptide is a characterized mouse model of MS. The pathology in this EAE model reflects those characteristic of MS. Previously we showed that in chronic EAE retinal ganglion cell loss occurs and increase of IL-17 and IFN-∂ in the optic nerve. There are some studies describing the effect of MS and EAE in the optic nerve; the impact on the retina is still not well characterized. Previously we showed that 7,8-Dihydroxyflavone (7,8-DHF) is a TrkB agonist, reduces the clinical severity in EAE mice spinal cord. Now we are showing that DHF is effective in ON in EAE mice. DHF treatment (5mg/kg 7,8-DHF/day/mouse; intraperitoneally) at onset of EAE symptoms significantly decreased the severity of ON in EAE mice. DHF decreased the infiltration and inflammation in EAE mice. Treatment with DHF decreased the CD20, CD3, CD45 and CD11b cell infiltration and also decreased the demyelination (LFB and MBP) in EAE mice optic nerve. Inflammatory markers IL-17, TNFα, iNOS, and ET-1 are significantly reduced with DHF treatment. These results will represent the effectiveness of DHF in reducing the ON in EAE and might be useful in MS patients with ON.

Disclosures: M.I. Arvas: None. **P.R. Guda:** None. **T.K. Makar:** None. **D. Trisler:** None. **C. Bever:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.07/W9

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant DA007606

Title: Alcohol drinking enhances methamphetamine-induced toxicity through inflammation

Authors: *A. L. BLAKER[1,2], B. K. YAMAMOTO[1]
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Abstract: Alcohol and methamphetamine (Meth) are often co-abused, and individually act on both dopamine and serotonin systems to cause long-term deficits in neurotransmission. However, the effects of co-morbid abuse on the brain are still unknown. We hypothesized that alcohol drinking would enhance the neurotoxicity typically observed after binge Meth use. Male Sprague Dawley rats voluntarily drank 10% ethanol (EtOH) every other day for 4 weeks and were then exposed to a binge Meth paradigm. Intake and preference for EtOH increased over the 4 week drinking period and reached serum EtOH concentrations of 70.88±1.9 mg/dL. EtOH drinking alone increased circulating lipopolysaccharide (LPS) in serum (~300%) and brain (~750%), as well as cyclooxygenase-2 (COX-2; ~50%), measured at 24 hr after the last day of drinking. Seven days after Meth exposure, decreases in dopamine (~50%) and serotonin (~40%) content and their plasmalemmal transporters (~45% and ~30%, respectively), were observed in the striatum. EtOH alone did not change dopamine or serotonin content and transporters but the serial exposure to EtOH and Meth exacerbated the depletions of dopamine (~95%) and serotonin (~75%), and decreases in dopamine (~90%) and serotonin (~70%) transporter immunoreactivities, indicating a synergistic relationship between the two drugs. The amount of EtOH consumed negatively correlated with the changes in dopamine and serotonin content and transporter immunoreactivities. The COX inhibitor, ketoprofen, administered during EtOH drinking alone did not alter EtOH intake, but blocked the increases in LPS and COX-2 typically observed after EtOH. COX inhibition also blocked the enhanced depletions of monoamines and their transporters observed 7 days after Meth in rats that drank EtOH. This implicates inflammation produced by voluntary EtOH drinking as a key mediator in the synergistic neurotoxic relationship between EtOH and Meth. Future studies will examine the potential influence of glutamate-mediated excitotoxicity in contributing to both inflammation and decreases in neurotransmitter content after EtOH+Meth.

Disclosures: A.L. Blaker: None. **B.K. Yamamoto:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.08/W10

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: VIEP-BUAP 2015-2017 give to I. D. Limon

CONACYT-MEXICO 169023 give to I.D, Limon

Title: The neuroinflammation-induced by the administration amyloid-β (25-35) in hippocampus of rats induce expression of galectin-1 and galectin-3

Authors: *E. RAMIREZ[1], C. SANCHEZ-MALDONADO[2], I. D. LIMON[2]
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Abstract: The administration of $A\beta_{25-35}$ peptide into the hippocampus of rats is able to cause memory impairment by increases the inflammatory response. However, the molecular mechanisms in the inflammatory process are unclear. Galectins play an important role as mediator in pathological inflammatory processes. Galectin 1 (Gal-1) has been associates with the inhibition of proliferation of astrocyte and Galectin 3 (Gal-3) with the activation microglia under various inflammatory conditions. Our aim was to evaluate if the neuroinflammation-induced by the administration amyloid-β (25-35) in hippocampus of rats induces expression of galectin-1 and galectin-3. We examined the spatial memory in the Morris water maze. After behavioral test the hippocampus was assessed for astrocytes (GFAP), microglia (Iba1), Galectin-1 (Gal-1) and Galectin-3 (Gal-3) by immunohistochemical, and moreover identification of IL-1β, TNF-α and IFN-γ by ELISA analysis. The administration of $A\beta_{25-35}$ impaired the spatial memory in the Morris Water Maze. The neuroinflammation evoked by $A\beta_{25-35}$ impaired spatial memory, because animal showed in a 30% ($p<0.01$) a major time to find the platform during the task respect to control group. Our results showed an increase of reactive gliosis (104% GFAP and 45% Iba1) in the hippocampus of $A\beta_{25-35}$ treated rats ($p<0.001$), associated whit the increased of cytokines IL-1β (139%, $p<0.001$), TNF-α (187%, $p<0.01$) and IFN-γ (36%, $p<0.05$) respect to control group. The number of cells positive to Galectins was detected predominantly in the cells of microglia-Gal-3 (109%) ($p<0.01$) and astrocytes-Gal-1 (103%) ($p<0.01$) respect to control group. Therefore, we suggest that Gal-1 and Gal-3 is involved in the inflammatory process induced by administration of the $A\beta_{25-35}$. Gal-1 is mainly produced by activated astrocytes, and can attenuate injuries. Gal-3-expressing microglia may be involved in the peak phase of the inflammatory response, in neurodegenerative process induced by $A\beta_{25-35}$ peptide.

Disclosures: E. Ramirez: None. **C. Sanchez-Maldonado:** None. **I.D. Limon:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

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Program#/Poster#: 050.09/W11

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Conacyt Grant 122 and 188565 to CGE

Conacyt Grant 241911 to FPS

Title: Increased serum levels of TNF in R6/1 mice and diminished inflammatory mediator secretion in Huntingtin-defective mast cells

Authors: *M. J. PÉREZ RODRÍGUEZ[1], P. MARTINEZ GOPAR[1], A. IBARRA SANCHÉZ[1], C. GONZÁLEZ ESPINOSA[1], F. PÉREZ SEVERIANO[2]
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Abstract: Recent evidence in patients with Huntington's disease (HD) suggests that mutated huntingtin (mHtt) modifies the immune cell function, contributing to the pathology. In particular, defective vesicular transport in immune cells could contribute to the progression of HD. However, the role of this protein in the cytokine secretion process of mast cells (MC) and the contribution of MC to HD in vivo has not been elucidated. The main objective of this work was to study the participation of Htt in the processes of secretion of inflammatory mediators in mast cells. Characterization of bone marrow-derived mast cells (BMMCs) from transgenic mice expressing mHtt (line R6/1) was performed by transmission and scanning electron microscopy, together with toluidine blue staining. Expression of the high affinity IgE receptor (FcεRI) and Toll-like receptor (TLR) 4 was evaluated by flow cytometry. Secretion of inflammatory mediators by anaphylactic degranulation or the constitutive pathway was evaluated measuring the release of of β-hexosaminidase after FcεRI triggering or TNFα, IL-6 and CCL-2 after TLR-4 activation using LPS. The results show that similar shape, size and receptor expression were found in both types of BMMCs, mHtt does not modify the anaphylactic secretion pathway but mHtt-expressing BMMCs secreted significantly less *de novo* synthesized cytokines by stimulating the constitutive secretion pathway with bacterial lipopolysaccharide (LPS). R6/1 mice secreted more TNF in serum than their WT littermates. Obtained results indicate that Huntingtin is not determinant for the differentiation of mast cells obtained from mouse bone marrow but it has a differential role in the secretion of different mediators released by the mast cell. Also, data suggests that Htt is involved in the intracellular mechanism that leads to the secretion of *de novo* synthesized TNF, IL-6 and CCL-2 following stimulation of the TLR4 receptor.

Disclosures: M.J. Pérez Rodríguez: None. **P. Martinez Gopar:** None. **A. Ibarra Sanchéz:** None. **C. González Espinosa:** None. **F. Pérez Severiano:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.10/W12

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CAPES

Title: Effect of glucose availability on cognitive performance and neurodegeneration process after status epilepticus

Authors: *I. S. MELO[1], A. L. D. PACHECO[1], Y. M. O. SANTOS[1], M. A. COSTA[1], V. O. SILVA[1], C. M. B. CAVALCANTE[1], J. FREITAS-SANTOS[1], M. DUZZIONI[1], R. SABINO-SILVA[2], A. U. BORBELY[1], O. W. CASTRO[1]
[1]Phisiology and Pharmacol., Federal Univ. of Alagoas, Maceio, Brazil; [2]Physiol., Federal Univ. of Uberlândia, Uberlândia, Brazil

Abstract: Glucose is the main energy substrate for the brain and its lack can lead to neuronal dysfunction. During *status epilepticus* (SE), the neurons become overexcited, increasing energy consumption. Therefore, a supply of glucose may prevent neuronal damage and memory consolidation caused by SE. Here we evaluated the effect of glucose availability in the memory consolidation, behavior of limbic seizures and neurodegeneration process. Experimental procedures were approved by the Ethical Committee for Animal Research of UFAL (04/2016). Male Wistar rats (n=35 [240-340g]) were submitted to stereotaxic surgery for implantation of a cannula in the hilus of dentate gyrus of hippocampus. Animals VEH+PILO and GLU+PILO received microinjections of vehicle (VEH, saline 0.9%, 1μL) or glucose (GLU, increases SGLT expression, 2 or 3mM), respectively, in hippocampus followed 30 minutes later by pilocarpine (PILO) (1.2mg/μL). In addition, PILO+GLU received GLU (2 or 3mM) after 5 minutes of PILO. After recovery from surgery, some animals were trained in inhibitory avoidance and were tested one day later. Behavioral analysis of seizures was performed for 90 minutes, according to Racine scale (1972). Animals were perfused 24 hours after SE and neurodegeneration was evaluated by histochemistry of Fluoro-Jade (FJ). FJ positive neurons (FJ+) were counted (ImageJ-NIH) in dorsal, medial and ventral hippocampus. Results were expressed as mean±SEM, compared by unpaired t test and one-way ANOVA followed by post-hoc test Student-Newman-Keuls. The administration of glucose (2 mM) prior to PILO did not reverse the damage in memory consolidation caused by PILO-induced SE. However, when administered shortly after PILO, glucose (2 mM) preserved memory consolidation. GLU+PILO (2mM) had higher number of WDS (120±12) and class 4 (33±9.9) than VEH+PILO (WDS, 61±17; class 4, 15±2.5). On the other hand, PILO+GLU (3mM) had fewer classes 3 (3±1.4) and 4 (4.1±3.2) than VEH+PILO (class 3, 14.9±2.5; class 4, 15.1±2.5), indicating a decrease of seizure severity. Total FJ+ neurons in CA3 (405±44) and CA1 (457±35) of hippocampus were higher in GLU+PILO 2mM than VEH+PILO (CA3, 235±52; CA1, 284±46). However, FJ+ total neurons decreased in the hilus (28±10) and CA1 (61±32) of PILO+GLU 2mM compared to VEH+PILO (Hilus, 129±32; CA1, 284±46). Similarly, PILO+GLU 3mM presented the same reduction pattern in hilus (30±9.7) and CA1 (61±28.5) when compared to the control group. Together, these preliminary data suggest that possibly the administration of intrahippocampal glucose promotes improvement of memory and protects brain against cell death in the earlier stage of epileptogenic processes.

Disclosures: I.S. Melo: None. **A.L.D. Pacheco:** None. **Y.M.O. Santos:** None. **M.A. Costa:** None. **V.O. Silva:** None. **C.M.B. Cavalcante:** None. **J. Freitas-Santos:** None. **M. Duzzioni:** None. **R. Sabino-Silva:** None. **A.U. Borbely:** None. **O.W. Castro:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.11/W13

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: FDA protocol E7579.01

Title: Microglial activation and vascular responses that are associated with thalamic neurodegeneration due to thiamine deficiency

Authors: *J. F. BOWYER[1], K. M. TRANTER[1], S. SARKAR[1], L. C. SCHMUED[1], J. P. HANIG[2]
[1]Neurotoxicology, Natl. Ctr. for Toxicological Res. Div. of Neurotoxicology, Jefferson, AR; [2]Office of Testing & Res. , MD-20993, CDER/ FDA, White Oak, MD

Abstract: Thiamine/ vitamin B1 deficiency can lead to Wernicke's encephalopathy and Wernicke-Korsakoff Syndrome (WKS) in humans, which is likely due to vascular leakage and neuronal degeneration in the diencephalon. However, the time course of the progression of these changes has not been fully characterized. Therefore, in this study, the progression of: 1) activated microglial association with vasculature; 2) neurodegeneration; and 3) any vascular leakage in the forebrain during the progress of thiamine deficiency were determined. A thiamine deficient diet along with 0.25 mg/ kg/ d of pyrithiamine was used as the mouse model. Vasculature was identified with Cd-31 and microglia with Cd-11b and Iba1 immunoreactivity. Neurodegeneration was determined by FJc labeling. The first sign of activated microglia within the thalamic nuclei were detected after 8 d of thiamine deficiency, and by 9d activated microglia associated primarily with vasculature were clearly present only in thalamus. At the 9 d time point there was minimal or no neurodegeneration present in thalamus. After the 10 d time point, clear evidence of neurodegeneration (FJc+ neurons) was seen only in the thalamus but the number of degenerating neurons was only 10% of the activated microglia. At 10 d, but not 8 d and 9 d, there were a few instances of IgG present in brain due to vascular leakage. Extravascular Fluoro-Gold accumulation was found in the same area as the IgG in thalamus, when it was given prior to sacrifice at 10 d. None of the animals at 10 d showed behavioral signs of seizure activity. Either dizocilpine (0.2 to 0.4 mg/ kg) or phenobarbital (10 to 20 mg/ kg) was administered to groups of mice from day 8 through day 10 in an attempt to block neurodegeneration. The phenobarbital had no effect and the MK-801 paradoxically enhanced neurodegeneration. In summary, activated microglia started surround vasculature 2 d prior to the start of neurodegeneration. This microglial response may be a means of controlling or repairing vascular leakage and/ or damage. Neurodegeneration is not likely due to glutamate excitotoxicity or vascular leakage; at least before behavioral seizure activity occurs, during thiamine deficiency. However, failure of

damaged vasculature endothelium to supply sufficient nutrients to neurons could still be contributing to the neurodegeneration. **Disclaimer** The contents of this manuscript do not necessarily reflect the views and policies of the U.S. Food and Drug Administration, nor endorsement of the mention of trade names or commercial products.

Disclosures: J.F. Bowyer: None. **K.M. Tranter:** None. **S. Sarkar:** None. **L.C. Schmued:** None. **J.P. Hanig:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.12/W14

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: EY026662

Title: The effect of Nrf2 transcription factor knock-out on glaucoma

Authors: *A. JASSIM-JABOORI, D. M. INMAN
Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH

Abstract: Glaucoma is the second leading cause of blindness. It drives a progressive and irreversible neuropathy of the optic nerve (ON) and eventually the degeneration of retinal ganglion cells (RGCs) somas in the retina. Nrf2, a transcription factor and a key regulator of antioxidant levels through the activation of genes containing the antioxidant response element (ARE), may have an important role in combating oxidative stress in glaucoma. We sought to determine the degree to which the Nrf2-ARE contributes to RGCs survival by subjecting wildtype and Nrf2-knockout (Nrf2-/-) mice to acute glaucoma injury. Acute glaucoma injury was achieved with 1µL injections of 8µm magnetic beads into the anterior chamber to induce blockage of aqueous humor outflow (beads occlusion model). Baseline (before injection) and weekly intraocular pressure (IOP) was measured. After 4 weeks, mice were sacrificed and tissue processed for total glutathione (GSH), a major cellular anti-oxidant, in retina and ON. In addition, immuno-labeling of RGCs using RNA binding protein with multiple splicing (RBPMS) was performed to determine the number of surviving retinal ganglionic cells. Both wildtype and Nrf2-/- mice, when subjected to the bead occlusion model, had highly significant IOP increase ($t= +9.30$, $p<0.001$) compared to control (no beads injection) of both Nrf2-/- and wildtype mice regardless of genetics ($t= +1.34$, $p>0.05$) and gender ($t=1.26$, $p>0.05$). Both wildtype and Nrf2-/- mice subjected to the bead occlusion model had significantly lower RGCs density than control mice ($t= -2.26$, $p<0.05$) regardless of gender ($t=0.91$, $p>0.05$). GSH levels in retina of glaucoma mice were significantly down-regulated ($t= - 2.68$, $p<0.01$) regardless of gender ($t=1.07$, $p>0.05$). GSH levels in ON were non-significant among groups (glaucoma $t= -1.55$, genetics $t= -$

0.39, and gender t= 0.86, all p>0.05). The rise in IOP and the down-regulation of GSH levels in both wildtype and Nrf2-/- suggest the accumulation of reactive oxygen species (ROS). Nrf2 may have an effect on the progression of glaucoma. Compensation from other Nrf transcription factors such as Nrf1 may play a role in the defense mechanism against ROS accumulation in glaucoma. Additional studies will be required to fully delineate the effect of Nrf2 on glaucoma.

Disclosures: A. Jassim-Jaboori: None. **D.M. Inman:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.13/W15

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Monomethylarsonous acid (MMAIII) increases rat brain microvascular endothelial cells (rBMEC) monolayers permeability by decreasing the tight junction proteins claudin-5 and occludin

Authors: *C. ESCUDERO-LOURDES[1], H. ROSAS-HERNÁNDEZ[2], E. Y. CUEVAS[2], S. F. ALI[2]
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Abstract: The blood-brain barrier (BBB)'s low permeability is mainly given due to tight junctions (TJs) located between the endothelial cells, which consist of interactions between the transmembrane proteins claudin-5 and occludin as well as with the intracellular proteins zonula occludens-1 and-2 (ZO-1, ZO-2). A change in BBB permeability is associated with the development and progression of different neurological pathologies. The trans-endothelial electrical resistance (TEER) of an in vitro model of BBB is a quantitative measure of the barrier integrity. Interestingly, inorganic arsenic (iAs) is considered a risk factor for cognitive impairment and neurodegenerative diseases in exposed populations around the world. iAs decreases the permeability of different endothelial cells by decreasing claudin and occludin proteins expression and consequently the TEER; however its effect on BBB has not been described yet. We propose that MMA^{III} could impair BBB through the negative modulation of the endothelial TJ's proteins, increasing its permeability. To evaluate this hypothesis, we determined TJs proteins expression, the TEER and the permeability in rat microvascular endothelial cells (rBMECs) monolayers that were exposed to different concentrations of the monomethylated metabolite of iAs (MMA^{III}). Results showed a significant decrease in claudin-5 and occludin proteins as wells as in the TEER of rBMEC monolayers that were exposed to 50, 100 and 200 nM MMA^{III} . These results were consistent with a significant increase of the

rBMEC monolayers permeability. Our observations strongly suggest that MMA^{III} could impair the BBB integrity through the down-regulation of the Tjs proteins of the endothelial cells.

Disclosures: C. Escudero-Lourdes: None. **H. Rosas-Hernández:** None. **E.Y. Cuevas:** None. **S.F. Ali:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.14/W16

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: 7,8-Dihydroxyflavone treatment shifts M1,M2 polarization and reduces the inflammation in experimental autoimmune encephalomyelitis

Authors: P. R. GUDA[1], M. I. ARVAS[2], T. K. MAKAR[2,3,4], *D. TRISLER[2,3,4], C. BEVER, Jr[3]
[1]Neurol., Univ. of Maryland, Baltimore, MD; [2]Dept Neurol., Univ. Maryland Sch. Med., Baltimore, MD; [3]VA medical center, Baltimore, MD; [4]VA Multiple Sclerosis of Excellence, Baltimore, MD

Abstract: We have studied the therapeutic effect and anti-inflammatory mechanisms of 7,8-Dihydroxyflavone (7,8-DHF) in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS). Recently, we showed that treatment with TrkB agonist 7,8-DHF starting from the induction of EAE attenuates neuroinflammation and clinical severity of disease (Makar.et.al. 2016 Neuroinflammation). Here we report new data with 7,8-DHF treatment during onset of EAE. Treatment (5mg/kg 7,8-DHF / per day/mouse; intraperitoneally) starting at onset of the disease significantly improved clinical symptoms and reduced inflammation in lumbar spinal cords. Similar to the reported findings with treatment at the induction of EAE, treatment with 7,8-DHF at disease onset, inhibited expression of Endothelin-1 (ET-1). Progression of the EAE was associated with significant infiltration into the parenchyma of spinal cords macrophages with M1 activation state that are pro-inflammatory. Treatment with 7,8-DHF reduced the number of M1 macrophages (Active state macrophages) and increased the number of M2 macrophages (Alternatively activated macrophages). This resulted in increased labeling for M2 markers, CD163 and reduces in M1 markers, CD83. The polarization of macrophages towards the M2 active state in 7,8-DHF treated mice was associated with decrease of the inflammatory molecules NFkB, iNOS, MCP-1 and ET-1. The results of the study revealed novel cellular mechanisms involved in anti-inflammatory effects of 7,8-DHF. The beneficial effect of 7,8-DHF by shifting the macrophage polarization towards M2, observed in EAE strongly indicates that treatment with TrkB agonists have promising therapeutic potential as disease modifying approach at onset of MS.

Disclosures: **P.R. Guda:** None. **M.I. Arvas:** None. **T.K. Makar:** None. **D. Trisler:** None. **C. Bever:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

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Program#/Poster#: 050.15/W17

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 2 R25 NS080687-06

Title: Early effects of SIV on neural markers of the prefrontal cortex in female macaques

Authors: *A. DIAZ ROSADO[1], A. MENDEZ[2], A. C. SEGARRA[3]
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Abstract: The Human Immunodeficiency Virus is a lentivirus that causes Acquired Immunodeficiency Syndrome (AIDS). Although treatment with antiretroviral agents has increased the rate of survival of these patients, HIV still has dreadful consequences, and the nervous system is among those greatly affected. Among infected patients, 33% will develop HIV Associated Neurocognitive Disorder (HAND), but the mechanisms involved are largely unknown. To address this issue, we studied the brains of females Rhesus Macaques infected with the Simian Immunodeficiency Virus Mac251 (SIVmac251) and sacrificed at day 41. We hypothesized that at this early stage, brains infected with SIV would show a decrease in synaptic contacts, and an increase in reactive astrocytes.
The Prefrontal Cortex (PFC), an area associated with higher cognition and abstract thinking, was dissected from macaques that at the time of death had in plasma a high viral load, low viral load or were SIV free (n=3/group). Using Western Blot quantification, we performed a triplicate of each of our proteins of interest, measuring the following neural synaptic markers: (1) Post-synaptic density 95 (PSD-95) and (2) Synaptophysin; a brain injury marker: (3) Glial fibrillary acidic protein (GFAP) and a neuroprotective marker (4) Estrogen receptors (ER).
We did not observe significant difference between our synaptic, brain injury or neuroprotective markers between our three groups (HVL, LVL, Control), although a trend. Nonetheless, macaques with a low viral load (LVL) showed levels of PSD-95 between high and SIV free macaques**.** These preliminary results indicate no differences in the synaptic proteins measured between high, low and SIV free PFC brain tissue 40 days after SIV infection, which suggest that early stages of SIV infection are not associated with synaptic damage. Lack of change in GFAP supports previous findings indicating that gliosis is present during late stages of HIV infection, those associated with encephalitis. We are currently investigating other brain areas, such as the

basal ganglia, and measuring viral load in brain tissue to determine how well they correlate with those in plasma.

Disclosures: **A. Diaz Rosado:** None. **A. Mendez:** None. **A.C. Segarra:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.16/W18

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: DTRA Grant CB3943

Title: The role of IL-1 signaling in neuroinflammation after soman-induced convulsions and anakinra treatment in mice

Authors: *T. M. FERRARA-BOWENS[1], J. K. CHANDLER[1], J. F. IRWIN[1], K. LAITIPAYA[1], A. V. MORAN[1], D. D. PALMER[1], M. D. WEGNER[2], E. A. JOHNSON[1]
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Abstract: Brain injury resulting from status epilepticus (SE) induced by soman (GD) stimulates peripheral macrophages and leukocytes, and microglia and astrocytes to overexpress neurotoxic cytokines, including interleukin-1 (IL-1), resulting in a neuroinflammatory response. IL-1 binds to the IL-1 receptor (IL-1R1) to initiate IL-1 signaling by activating various kinase pathways, including NFκB, which signals the release of IL-6 and TNFα. The IL-1R1 is inhibited by the IL-1 receptor antagonist (IL-1Ra), which competes with IL-1 for binding to the IL-1R1. Although the presence of IL-1, IL-6, and TNFα has been reported after GD-induced SE, the role of IL-1 signaling in the neuroinflammatory response has not been investigated post exposure in knockout (KO) mice. The purpose of these studies was to determine cytokine expression levels of IL-1, IL-6, and TNFα after GD-induced convulsions in wild type (WT), IL-1R1 KO, and IL-1Ra KO mice, and anakinra treatment in exposed WT mice. Results showed early upregulation of IL-1 followed by later downregulation in the KO strains, as well as IL-1 signaling early and later after anakinra treatment. Additionally, IL-6 upregulation was found between 3 and 12 hours in KO mice, whereas TNFα expression was prominent later in WT mice. These results show the regulatory function of IL-1 regarding neuroinflammation after GD-induced convulsions. Additionally, targeting the IL-1 signaling pathway with anakinra changes cytokine expression, and therefore, the neuroinflammatory response. The views expressed in this talk 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 and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. These studies were funded by the Defense Threat Reduction Agency (DTRA).

Disclosures: T.M. Ferrara-Bowens: None. **J.K. Chandler:** None. **J.F. Irwin:** None. **K. Laitipaya:** None. **A.V. Moran:** None. **D.D. Palmer:** None. **M.D. Wegner:** None. **E.A. Johnson:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.17/W19

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Copaxone decreases the inflammation and endoplasmic reticulum stress in experimental autoimmune encephalomyelitis

Authors: *K. SAWHNEY[1], M. I. ARVAS[1], P. R. GUDA[1], V. SHUKLA[1], D. TRISLER[1,2,3], C. BEVER, Jr[2,3], T. MAKAR[1,2,3]
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Abstract: Background: Multiple sclerosis (MS) is an inflammatory autoimmune disease that attacks the central nervous system (CNS), resulting in demyelination, axonal damage and neuronal loss. MS is one of the most common chronic neurological diseases in young adults. The most intensively studied model of MS is experimental autoimmune encephalomyelitis (EAE).Copaxone (Glatirmer acetate) is an established drug for MS treatment. Previously showed that copaxone decreases the clinical severity and demyelination. Here we are showing that copaxone decreases the inflammation by decreasing the inflammatory markers. We also show that copaxone decreases the endoplasmic reticulum stress in EAE mice spinal cord. **Methods:** We induced EAE in 2 groups of C57B1/6 mice by immunization with myelin oligodendroglial protein peptide 35-55. One EAE group of mice was treated with copaxone, 2mg/kg/day/mouse; subcutaneously, starting on the day of symptom onset. We euthanized the mice on day 40 from EAE induction and studied spinal cord by immunohistochemically and by western blot. **Results:** Copaxone treatment significantly reduced the pro inflammatory markers, IL-17, TNFα and IFNγ in EAE mice spinal cord. It also increased the IL-10, anti-inflammatory marker in EAE mice. In electron microscopic pictures, copaxone decreased the endoplasmic reticulum disruption in EAE mice. Endoplasmic reticulum stress (ER-stress) markers, CHOP and PERK, are increased in EAE mice spinal cord. These are reversed with copaxone treatment. **Conclusion:** Endoplasmic reticulum stress is increased in EAE mice but copaxone is effective in reducing it along with decreasing the inflammation.

Disclosures: **K. Sawhney:** None. **M.I. Arvas:** None. **P.R. Guda:** None. **V. Shukla:** None. **D. Trisler:** None. **C. Bever:** None. **T. Makar:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS-1K08NS094683-01

NINDS-K12NS066225 - 01A2

Child Neurology Foundation

Title: Human and mouse endothelium have different lipid metabolism consequences after silencing of ABCD1

Authors: ***A. BERENSON**[1], N. SASIDHARAN[1], M. VISSERS[1], A. MOSER[2], P. L. MUSOLINO[1], F. EICHLER[1]
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Abstract: X-linked adrenoleukodystrophy (ALD) is a debilitating neurological disorder caused by mutations in the peroxisomal half transporter ABCD1, which is essential for the import of very long chain fatty acids (VLCFAs) such as C26:0-CoA, C24:0-CoA, and C22:0-CoA from the cytosol. Mouse knockouts of *ABCD1* are protected from cerebral ALD (CALD), the severe inflammatory phenotype observed in 60% of male patients, but the reason for this remains unknown. We postulated that the observed differences in human vs mouse phenotypes lay upon distinct regulation of brain microvascular endothelium following loss of ABCD1 function. We previously observed that, 48 hours after *ABCD1* silencing, HBMECs display decreased levels of tight-junction protein Claudin5, as well as increased monocyte adhesion and transmigration, while ABCD1-deficient MBMECs did not display this phenotype. To further elucidate differences in endothelial response to loss of ABCD1, we compared lipid profiles of HBMECs and MBMECs 48 hours after *ABCD1* silencing. Interestingly, at this time point VLCFA levels were elevated only in mouse endothelium, while plasmalogen depletion was observed only in human endothelium. These findings support our previous observation that endothelial dysfunction precedes VLCFA elevation in human brain endothelium suggesting other mechanisms regulate tight-junction protein expression, adhesion, and transmigration. Additionally, the human-specific decrease in PE plasmalogen levels may contribute to the dysfunction that appears to be absent in mouse endothelium. Understanding these differences

may unravel the mechanisms underlying the conversion to cerebral ALD and provide new insights for the generation of a mouse model and novel therapeutic approaches.

Disclosures: A. Berenson: None. **N. Sasidharan:** None. **M. Vissers:** None. **A. Moser:** None. **P.L. Musolino:** None. **F. Eichler:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.19/W21

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Restraint stress augmented the MPTP-induced Parkinson's disease like syndrome in mice via provoking inflammatory and apoptotic pathway: A TrκB agonist neuroprotective mechanism

Authors: *M. KWATRA[1], S. AHMED[2], V. NAIDU[2], M. LAHKAR[2]
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Abstract: Parkinson disease (PD) is a debilitating motor disorder affected a million populations worldwide. The objective of our study was to investigate the effect of TrkB agonist; 7,8-dihydroxyflavone (7,8-DHF) on 6-hydroxydopamine (6-OHDA) induced inflammation cascade in Neuro-2a (N2a), RS and MPTP-induced neuroinflammatory cascade followed by apoptotic signaling in the substantia nigra and striatum region of C57bl/6 male mice (weight 25-30g). The Neuro-2a (N2a) cells treated with 6-OHDA of various concentrations (1.5-100 μM) for 24 hrs and cytotoxicity (6-OHDA, 25 μM) was prevented by 7,8-dihydroxyflavone (3, 6 and 12 μM) evaluated by MTT and LDH assay. The neuroinflammatory markers (NF-κB and Cox-2), as well as apoptotic markers (Bax, Bcl-xl, Bcl-2, cytochrome C) protein expression, were markedly upregulated by 6-OHDA treatment which further attenuated with 7,8-DHF co-treatment. Further, the *in-vivo* experiment was carried out with restraint Stress (6 h per day for 28 days) and MPTP (30 mg/kg, i.p. treatment for 5 days i.e 10^{th} day to 14^{th} day) treatment. The group with combined restraint stress and MPTP were found with severe motor impairment evaluated on rotarod test, open field test, and grip strength test. The 7,8-DHF (10 mg/kg, i.p. treatment for 28 days) significantly ameliorated the symptoms in Restraint Stress, MPTP-treated animals induced motor deficits. The biochemical oxido-nitrosative stress markers (MDA, nitric oxide level and reduced glutathione (GSH) level), proinflammatory cytokines (TNF-α, IL-1β level) in striatum and substantia nigra were found elevated in MPTP and RS+MPTP treated group. Furthermore, the real-time PCR for genes (NF-κB, Cox-2, iNOS, Nrf2) and western blot for the protein expression studies were found to be altered in the striatum (NF-κB, Nrf2, P53, Bax, Bcl-xl, Bcl-2, cytochrome C, cleaved caspase 3, tyrosine hydroxylase) and substantia nigra (NF-κB, Nrf2, P53, Bax, Bcl-xl, Bcl-2, cytochrome C, cleaved caspase 3, tyrosine hydroxylase) of animals got

reversed with 7,8-DHF treatment. Hence, 7,8-dihydroxyflavone (TrκB agonist) with its *in-vitro and in-vivo* neuroprotective and anti-apoptotic potential may be the future candidate for the future prevention of Parkinson's disease progression.

Disclosures: M. Kwatra: None. **S. Ahmed:** None. **V. Naidu:** None. **M. Lahkar:** None.

Poster

050. Neuroinflammation

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Program#/Poster#: 050.20/W22

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Natural Science Foundation of China (31571408 and 81601065)

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Title: AdipoR agonist, AdipoRon, suppresses myelin lipid accumulation and ameliorates macrophage infiltration after spinal cord injury

Authors: *K. XIANG[1], A. LI[2], C. QIN[2], Y. REN[3], X. SUN[2]
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Abstract: Myelin-laden macrophages (mye-Φ), resulting from phagocytosis of myelin debris by infiltration of bone marrow-derived macrophages, are abundantly present in spinal cord injury (SCI). The accumulation of myelin debris in these macrophages induces neuroinflammation, contributing to neurodegeneration after SCI. Lipids are major components of myelin debris; therefore, efficient efflux of myelin lipid may help ameliorate macrophage functions. Adiponectin is a protein hormone that can increase cholesterol efflux from oxLDL-treated macrophages. In this study, we found that AdipoRon, a novel small molecule agonist of adiponectin receptors, could effectively decrease myelin lipid accumulation and suppress foam cell formation in mye-Φ. Such effects were mediated by APPL1/PPARγ/LXRα/ABCA1 pathway. AdipoRon treatment *in vitro* could inhibit the production of chemokines and then ameliorate the recruitment of naive macrophages by mye-Φ. Furthermore, *in vivo* administration of AdipoRon significantly prevented macrophage infiltration into injured spinal cord with alleviated neurodegeneration and improved motor function. These data suggest that AdipoRon

may be a promising therapeutic approach for the treatment of macrophage-mediated neuroinflammation in SCI.

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Poster

050. Neuroinflammation

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant F31NS095528

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Title: Comparison between sciatic nerve transection and sciatic nerve crush: Differences in regenerative outcomes peripherally, graded central neuroinmmune response and differences in spinal circuit plasticity following injury

Authors: *T. M. ROTTERMAN[1], K. P. MACPHERSON[2], T. CHOPRA[1], S. FISHER[3], M. G. TANSEY[4], F. J. ALVAREZ[1]
[1]Physiol., [3]SURE Program, [2]Emory Univ., Atlanta, GA; [4]Physiol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Peripheral nerve injury results in a robust central neuroimmune response followed by plasticity of essential spinal motor circuits. The extent of this plasticity depends on the severity of the injury sustained. One example is the loss of the stretch reflex following complete nerve transection while nerve crush results in a slight reflex enhancement. This reflex is mediated by monosynaptic connections between proprioceptive Ia afferents and homonymous motoneurons (MNs). We hypothesized that complete nerve transection would result in a greater loss in Ia afferent inputs and a more robust neuroinmmune response compared to crush. To investigate these differences, we performed sciatic nerve cut or crush injuries in transgenic mice expressing green fluorescent protein in resident microglia cells (CX3CR1-GFP) and red fluorescent protein in peripheral myeloid cells (CCR2-RFP). We then quantified the loss in Ia afferent inputs on pre-labeled lateral gastrocnemius MNs and compared the immune response, using histology and flow cytometry, in the lumbar spinal cord. Following transection there is a permanent 37% loss in Ia afferent inputs on MNs 8 weeks after injury, a time when motoneurons already reinnervated their targets. However, nerve crush did not result in permanent losses, even though a similar number of motoneurons and sensory afferents are axotomized. Following nerve injury, microglia cells in the ventral horn become activated and increase in number. Three days after injury both models showed a significant increase in the number of microglia cells (cut: 27%, crush 30%) however

while microglial cells are retained for up to 3 weeks following transection, their numbers are reduced one week after crush. The number of myeloid-derived CCR2+ cells that entered the spinal cord also differ between both models. Complete transection resulted in a significant increase in number of RFP+ cells in the ventral horn 2 and 3 weeks following injury, while there was little infiltration after nerve crush. We characterized the phenotype of these CCR2+ cells after sciatic transection and found they include different classes of T cells, dendritic cells, and macrophages. To better understand the role of these CCR2+ we performed sciatic nerve transections in CCR2 KO mice and this reduced the loss of Ia afferents on axotomized MNs, suggesting that CCR2-dependent mechanisms are involve in the removal of these inputs. In conclusion, we found that complete nerve transection results in a more robust and prolonged immune response which ultimately leads to the permanent loss of proprioceptive Ia afferent inputs on MNs.

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Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Bay Area Lyme Foundation (USA)

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ICT and Future Planning and Korea Mouse Phenotyping Project, the Ministry of Science (Korea) (2013M3A9D5072560)

Title: Bacterial lipopeptides disrupt neural activity and synaptic network by damaging presynapses in rodent models

Authors: *K.-M. KIM[1], Y. LEE[3], H.-R. LEE[2], A. I. ZAMALEEVA[1], M. INAYATHULLAH[1], T. D. PALMER[2], H.-Y. LEE[3], J. RAJADAS[1]
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Abstract: Neural damage induced by bacterial products involves non-specific symptoms, which is difficult to detect using laboratory tests that mainly address immunopathological abnormalities with low spatiotemporal resolution. To fully understand the pathological state of brain during bacterial infection, it is essential to investigate functional abnormalities over time. Here, we investigated the effect of Pam_3CSK_4 (PAM), a synthetic bacterial lipopeptide, on synaptic

dysfunction of mice brains and cultured neurons in parallel. [^{18}F]FMZ-PET imaging of mice brains injected with PAM (500 ng/ml) revealed that the synaptic integrity and network in the ipsilateral limbic system (i.e., region with strong presynaptic inputs) was aggravated for 7 days. In contrast, [^{18}F]FDG-PET imaging showed that the abnormal metabolic activity of neurons in the brain injected with PAM recovered during the same time period. *In vitro* neuron culture studies also demonstrated that PAM above 500 ng/ml decreased the density of presynaptic sites and the frequency of miniature excitatory postsynaptic current (mEPSC) whereas the amplitude of mEPSC was not altered by PAM. However, PAM did not induce neuronal apoptosis. These results suggest that PAM causes functional disorder in the brain by damaging presynapses rather than by disrupting metabolic activity of neurons. We also showed that PAM induced synaptic clustering, but not alter the expression of synaptic proteins (i.e., synapsin, PSD-95). In addition, physicochemical analysis using atomic force microscopy and dynamic light scattering showed that PAM has a high aggregating potential above the concentration that caused synaptic impairment. These results imply that PAM could damage synapses via post-translational mechanism, and the aggregation of PAM could be involved in synaptic disruption similarly to that of amyloid-beta in Alzheimer's disease or α-synuclein in Parkinson's disease.

Disclosures: K. Kim: None. **Y. Lee:** None. **H. Lee:** None. **A.I. Zamaleeva:** None. **M. Inayathullah:** None. **T.D. Palmer:** None. **H. Lee:** None. **J. Rajadas:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.23/W25

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT

Title: Determination the viability of a islets of langerhans hepatic portal graft in a murine model of type 1 diabetes mellitus

Authors: *B. UGALDE VILLANUEVA, I. IBARRA VALDOVINOS, R. RESENDIZ GUTIERREZ, M. SALGADO SALGADO, E. LÓPEZ ARVIZU, M. ABURTO FERNÁNDEZ, N. G. HERNÁNDEZ CHAN, H. L. HERNÁNDEZ MONTIEL
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Abstract: Introduction: Type 1 diabetes mellitus (T1D) is a metabolic disease caused by an autoimmune reaction that destroys the pancreatic beta cells, gradually decreasing the ability to produce insulin, leading to the development of chronic hyperglycemia. It is estimated that in 2015, around the world 542,000 children under 15 were suffering from T1D, and it is estimated an incidence of 86,000 new cases per year. In Mexico, the reported incidence up to 2010 was

6.2%, and according to the International Diabetes Federation, in our country around 13,500 children under 15 were suffering T1D in 2015. T1D treatment is based on exogenous insulin administration; however, glycemic control is often difficult due to the constant dose adjustment based on weight, making it difficult to prevent chronic complications. This has led to the constant search for new treatments to afford a better control of glycemia. One of the most promising alternatives is the graft of islets of Langerhans. This approach is used in humans, and patients have achieved independence of exogenous insulin administration for up to 5 years. However, the use of these techniques have some technical limitations as the process of islet isolation, insufficient amount of islets available for grafting, the adverse effect on the use of immunosuppressive agents and gradual loss of function as well as destruction of grafted islets, all of which limit their efficiency. **Objective:** Standardize and determine the viability of the graft of islets of Langerhans in a model of T1D with streptozotocin, treated with thiamine pyrophosphate (PPT) and an inducer of endogenous interferon. **Methodology:** the Obtaining an enriched concentrate of islets of Langerhans will be performed by Ficoll column separation which will be implanted in the portal circulation of diabetic Wistar rats treated with PPT and an endogenous interferon inducer. The levels of glucose and peptide C will be measured before and after grafting. Finally, a histological and immunohistochemical study will be performed to determine the viability of the islet graft of Langerhans. **Results:** Transplantation results obtained from the study will be reported. **Conclusion**: This work will allow us to set up therapies that improve the survival of the portal graft and also will allow us to evaluate the effect of transplantation in models of neurodegeneration.

Disclosures: B. Ugalde Villanueva: None. **I. Ibarra Valdovinos:** None. **R. Resendiz Gutierrez:** None. **M. Salgado Salgado:** None. **E. López Arvizu:** None. **M. Aburto Fernández:** None. **N.G. Hernández Chan:** None. **H.L. Hernández Montiel:** None.

Poster

050. Neuroinflammation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 050.24/W26

Topic: B.09. Physiological Properties of Neurons

Support: NSERC

Brain Canada

CONACyT

Title: Neonatal inflammation increases excitability in the pyramidal cells of mouse CA1 hippocampus in a sex and age dependent manner

Authors: *C. D. GÓMEZ MARTÍNEZ, S. ACHARJEE, Q. J. PITTMAN
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Abstract: Previous work by our research group suggests that early life systemic inflammation results in increased excitability in the adult brain. To unmask the mechanisms underlying such alteration, we investigated whether intrinsic membrane properties in adolescent and adult hippocampus neurons were altered as a consequence of early life inflammation. With this purpose, C57/BL6 mice were bred in house and male and female pups from multiple litters were injected with LPS (100 μg/kg *i.p.*) or vehicle (saline solution) at postnatal day 14 (P14), and kept until adolescence (P35-45) and adulthood (P60-70), when brain slices were prepared and whole-cell recordings were obtained from CA1 hippocampal pyramidal neurons. In neurons of adult male mice pretreated with LPS, the action potential threshold to a ramp current injection was hyperpolarized (-47±0.5 mV vs -42±0.94 mV), compared to neurons of the saline control group. This was associated with increase in the input resistance and in the number of action potentials elicited by depolarizing current pulses. Under voltage clamp, the amplitude of the H-currents was decreased in the LPS-pretreated animals compared to controls. In contrast, no significant changes were observed in any of the membrane properties mentioned above in the hippocampal neurons of adult female mice pretreated with LPS, or in adolescent mice, regardless gender. In conclusion, these findings demonstrate that neonatal inflammation leads to long term increased excitability in the adult male mouse hippocampus through changes in intrinsic membrane properties.

Disclosures: C.D. Gómez Martínez: None. **S. Acharjee:** None. **Q.J. Pittman:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.01/W27

Topic: C.08.Stroke

Support: AHA 16POST27790076

NIH R21 1R21NS094087-01

Title: Stem cells target stroke vasculome to confer vascular anti-inflammatory response

Authors: *S. A. ACOSTA[1], V. DE A. GUEDES[2], J. LEE[2], Y. KANEKO[2], C. V. BORLONGAN[2]
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Abstract: Stroke is the number one cause of disability in the adult population and the fourth leading cause of death in the United States. Currently, the therapeutic interventions are limited

with only one FDA-approved drug for ischemic stroke; namely tissue plasminogen activator or tPA. Recent findings revealed that cerebral endothelium secrete molecules, namely inflammation-associated vasculome. In the present study, we evaluated the therapeutic effect of endothelial progenitor cells on the inflammation-associated stroke vasculome. In vitro, human endothelial (HEN6)cells (HEN6) were prepared and grown for 10 days. qRT-PCR revealed that under ambient condition, baseline of the vasculomes BRM, IκB, foxf1, and ITIH-5 could be detected, but following oxygen glucose deprivation (OGD), there were significant elevations in all inflammation-associated stroke vasculome genes (p's<0.05 vs. respective level of each gene in ambient condition). Interestingly, co-culture of HEN6 with human EPCs during OGD treatment significantly blocked the elevations of BRM, IκB, and foxf1 (p's<0.05 vs. respective level of each gene in OGD condition), but not ITIH-5 (P>0.05). Next, employing the knockdown technology, silencing the inflammation-associated stroke vasculome gene, IκB, as opposed to scrambled knockdown, blocked the EPC-mediated protection of HEN6 against OGD (p's<0.0 vs. OGD or OGD+ IκB knockdown). In vivo, animals received intracerebral EPCs transplantation or vehicle into the striatum and cortex 4 hours post-ischemic stroke. Motor and neurological functions were assessed at baseline, post-ischemic stroke on Day 0,1,3,7,and 30 post EPC transplantation. Elevated body swing test, forelimb akinesia, and paw grasp test revealed significant amelioration of stroke-EPC animals at all-time points compared to stroke-vehicle animals (p's<0.01). Rotorod showed significant amelioration on motor function of stroke-EPC animals relative to stroke-vehicle animals up to Day 30 (p's<0.01). At 7 days post-transplantation, protein analysis and quantification of immunofluorescent intensity in cortex and striatum revealed significant downregulation of the stroke vasculome BRM, IKB, FOXF-1, ITIH-5, PMCA2 and MHCII+ cells of stroke-EPC animals compared to the stroke-vehicle animals (p's<0.0001). Further immunofluorescent intensity analysis revealed a significant elevation of RECA1 in the cortex and striatum of stroke-EPC animals relative to the stroke-vehicle animals (p's<0.01). In summary, stroke induced upregulation of inflammation-associated vasculome, which was attenuated by EPCs leading to amelioration of stroke-induced functional deficits

Disclosures: S.A. Acosta: None. **V. De A. Guedes:** None. **J. Lee:** None. **Y. Kaneko:** None. **C.V. Borlongan:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

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Program#/Poster#: 051.02/W28

Topic: C.08.Stroke

Support: R01NS081055

Title: Pericyte response during stroke recovery

Authors: *T. PHAM, S. CARMICHAEL
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Abstract: Stroke is the leading cause of adult disability. The brain has limited regenerative capacity after stroke. One of the most dramatic examples of neural repair after stroke is post-stroke neurogenesis - the production of new neurons in the area of damage. Stroke stimulates progenitor cells in the subventricular zone (SVZ) to divide and send more differentiated neuroblasts migrating to peri-infarct striatum and cortex. In the localization of neuroblasts in peri-infarct tissue there is a tight association with angiogenic vessels, forming a regenerative neurovascular niche after stroke. Pericytes, a type of perivascular cells, are a crucial component of this regenerative neurovascular niche. The central nervous system has the highest density of pericytes compared to other systems. Pericytes play diverse and crucial roles in the brain including maintenance of blood-brain barrier integrity, angiogenesis, and regulation of cerebral blood flow. Pericytes are also shown to react to tissue injury and possess mesenchymal properties. Outside of the brain, pericytes can replace tissue-specific cells such as odontoblasts, myocytes, myofibroblasts, adipocytes or indirectly mediate repair processes. However, the role of pericytes has not been thoroughly investigated in stroke, specifically in the peri-infarct tissue niche, mostly due to the lack of a good animal model or tools to genetically label pericytes in the brain. Here, we utilize a transgenic mouse model PDGFRb-Cre driving expression of tdtomato to label pericytes. Using multiple models of stroke, we analyzed the proliferative capacity of pericytes and their physical interaction with neuroblasts, angiogenic vessels, and oligodendrocytes precursor cells after stroke. We show that pericyte coverage in the cortex and white matter decreases significantly right after stroke. This loss of pericytes is compensated by a burst of pericyte proliferation, starting at 3 days, peaking at 7-14 days and persisting out to 1 month post-stroke. These findings serve as preliminary data for future studies investigating the roles of pericytes after stroke, and manipulation of pericytes to promote post-stroke recovery and repair. Supported by NIH R01NS081055.

Disclosures: T. Pham: None. **S. Carmichael:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.03/W29

Topic: C.08.Stroke

Title: Intravenous infusion of mesenchymal stem cells inhibits intracranial hemorrhage after recombinant tissue plasminogen activator therapy for transient middle cerebral artery occlusion in rats

Authors: *M. NAKAZAKI, M. SASAKI, Y. K. SASAKI, S. OKA, T. NAMIOKA, A. NAMIOKA, R. ONODERA, O. HONMOU
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Abstract: Objective; Reperfusion therapy with intravenous recombinant tissue plasminogen activator (rt-PA) is the standard of care for acute ischemic stroke. However, hemorrhagic complications can result. Intravenous infusion of mesenchymal stem cells (MSCs) reduces stroke volume and improves behavioral function in experimental stroke models. One suggested therapeutic mechanism is inhibition of vascular endothelial dysfunction. The objective of this study was to determine whether MSCs suppress hemorrhagic events after rt-PA therapy in the acute phase of transient middle cerebral artery occlusion (tMCAO) in rats. Methods; After induction of tMCAO, 4 groups were studied: 1) normal saline [NS]+vehicle, 2) rt-PA+vehicle, 3) NS+MSCs, and 4) rt-PA+MSCs. The incidence rate of intracerebral hemorrhage, both hemorrhagic and ischemic volume, and behavioral performance were examined. Matrix metalloproteinase-9 (MMP-9) levels in the brain were assessed with zymography. Quantitative analysis of regional cerebral blood flow (rCBF) was performed to assess hemodynamic change in the ischemic lesion. Results; The MSC-treated groups (Groups 3 and 4) experienced a greater reduction in the incidence rate of intracerebral hemorrhage and hemorrhagic volume 1 day after tMCAO even if rt-PA was received. The application of rt-PA enhanced activation of MMP-9, but MSCs inhibited MMP-9 activation. Behavioral testing indicated that both MSC-infused groups had greater improvement than non-MSC groups had, but rt-PA+MSCs provided greater improvement than MSCs alone. The rCBF ratio of rt-PA groups (Groups 2 and 4) was similar at 2 hours after reperfusion of tMCAO, but both were greater than that in non rt-PA groups. Conclusions; Infused MSCs may inhibit endothelial dysfunction to suppress hemorrhagic events and facilitate functional outcome. Combined therapy of infused MSCs after rt-PA therapy facilitated early behavioral recovery.

Disclosures: M. Nakazaki: None. **M. Sasaki:** None. **Y.K. Sasaki:** None. **S. Oka:** None. **T. Namioka:** None. **A. Namioka:** None. **R. Onodera:** None. **O. Honmou:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.04/W30

Topic: C.08.Stroke

Title: Efficacy of biomaterials augmentation of iPS immature glial cell transplantation after stroke

Authors: *G. N. PRASHANT[1], I. L. LLORENTE[2], E. SIDERIS[3], J. CINKORNPUMIN[4], T. SEGURA[3], W. E. LOWRY[4], S. T. CARMICHAEL[2]

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Abstract: Stroke is a leading cause of adult disability, with limited treatments options in the subacute and chronic time periods. There is a limited process of neural repair after stroke, characterized by neurogenesis, axonal sprouting, angiogenesis, and sensory and motor cortical remapping, particularly in the peri-infarct region. There has been recent interest in the potential for exogenous stem cell therapy to augment these endogenous mechanisms of recovery. In addition, stem cells may integrate into existing neural networks through differentiation into neurons and glial cells. As these processes of neural repair occur over the time span of weeks to months after stroke, they may provide treatment options for a wider array of patients. The transplantation of glial progenitor (GEPs) cells has not previously been studied in cortical stroke. We have shown that these cells differentiate into immature astrocytes, a cell type that has important roles in circuit formation in the developing brain. iPS-GEPs have specific characteristics that make them a promising therapeutic intervention for cortical stroke, namely, the ability to migrate over wide distances in the brain, promote formation of cortical connections, and enhance neurogenesis. In order to promote progenitor cell survival and differentiation, injectable hydrogels have recently been engineered to serve as a tissue scaffold that matches the mechanical properties of the surrounding brain. We have previously described a hydrogel suspension made up of a hyaluronic backbone with nanoparticles embedded with VEGF (hVc), which has demonstrated biocompatibility and promoted vascular infiltration in the infarct and peri-infarct regions. In this study we combined the novel use of iPS-GEP cells with an injectable hydrogel (hVc) in a murine model of cortical stroke. We transplanted hiPS-GEP cells embedded in a hydrogel to adult NSG mice at a subacute time point (7 days) after a photothrombotic stroke. iPS-GEP cellular survival, differentiation, and migration were assessed, and the effect of this therapy on the proliferation of immature neurons, astrocytes, and blood vessels was determined. The results from this study are important in further characterizing the role of glial progenitors in recovery after cortical stroke and highlighting the potential role for a structural hydrogel in this process.

Disclosures: G.N. Prashant: None. **I.L. Llorente:** None. **E. Sideris:** None. **J. Cinkornpumin:** None. **T. Segura:** None. **W.E. Lowry:** None. **S.T. Carmichael:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.05/W31

Topic: C.08.Stroke

Support: Canadian Institutes of Health Research (CIHR) (MOP-14828)

JGZ was supported by Postdoctoral fellowships from the Heart and Stroke Foundation of Canada.

AG was supported by a postdoctoral fellowship from the CIHR

Title: Microglia and macrophages differ in their inflammatory profile after permanent brain ischemia

Authors: *J. G. ZARRUK, A. D. GREENHALGH, S. DAVID
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Abstract: We studied the expression of pro- and anti-inflammatory molecules in microglia and infiltrating monocyte-derived macrophages after permanent Middle Cerebral Artery Occlusion (pMCAO). LysM-EGFP knock-in mice were used to distinguish between these two cell types, as peripheral myeloid cells are EGFP+, while microglia are not. This was confirmed with P2ry12 (a microglial specific marker), Iba-1 and EGFP immunostaining. The peak of $EGFP^+$ myeloid cell infiltration was 72h post-ischemia, and were distributed evenly in the lesion core, surrounded by a dense region of microglia. Flow cytometry showed that a higher percentage of microglia expressed TNF-alpha at 3 and 7 days post-pMCAO as compared to infiltrating macrophages. Microglia and macrophages were purified by fluorescence activated cell sorting 72h post-ischemia to assess the mRNA expression of inflammatory markers. Macrophages up-regulated mRNA expression of arginase-1 (Arg-1) by 1000-fold, and IL-1β by 90-fold as compared to microglia. At the protein level, a significantly number of macrophages express Arg-1, while few if any microglia expressed Arg-1. However, IL-1β protein was not detected in macrophages by flow cytometry or immunofluorescence labeling of tissue sections but was instead detected in astrocytes along the lesion border. A PCR-array screen of 84 inflammatory genes revealed that pro-inflammatory chemokines and cytokines were predominantly upregulated in macrophages but down-regulated in microglia in the ischemic brain. Our results show clear differences in the inflammatory expression profile between microglia and macrophages 72 hours post-ischemia which may shape repair and pro-regenerative mechanisms after stroke.

Disclosures: J.G. Zarruk: None. **A.D. Greenhalgh:** None. **S. David:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.06/W32

Topic: C.08.Stroke

Support: NIH Grant NS084744

NIH Grant NS095064

NIH Grant NS093446

AHA 14POST18720029

Title: Humanized sickle mice are sensitive to hypoxia/ischemia-induced stoke, but respond to tissue plasminogen activator treatment

Authors: *Y.-Y. SUN[1], J. LEE[1], H. HUANG[1], M. B. WAGNER[2], C. H. JOINER[2], D. R. ARCHER[2], C.-Y. KUAN[1]
[1]Dept of Pediatrics (Neurology), [2]Dept of Pediatrics, Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Stroke in sickle cell anemia (SCA) consists of silent cerebral infarct (SCI) and large overt stroke. There are areas for improvement in the current stroke management for SCA, while Townes humanized sickle mice (knock-in/out mice that express the human α, γ, and sickle-β hemoglobin genes) rarely exhibit spontaneous stroke and are too fragile to endure experimental stroke. Here we test the hypothesis that Townes sickle mice are sensitive to hypoxia-ischemia (HI)-induced stroke, but respond to tissue plasminogen activator (tPA). We report three sets of results. First, three-month-old sickle mice of the SS genotype (βS/βS) have a higher resistive index (RI), but normal flow velocity in the common carotid artery, than with AA (βA/βA) or AS (βA/βS) mice. SS mice were also also prone to repetitive-mild HI (rmHI)-induced cerebral infarct and mortality, whereas AA mice were resistant to rmHI. Second, 6-month-old SS mice developed elevated flow velocity and greater without stenosis of the carotid artery akin to those previously implicated in large overt stroke in SCA. Rather, SS mice showed ectopic P-Selection and plasminogen activator inhibitor (PAI-1) expression in cerebral blood vessels, suggesting a hyper-coagulation state. Finally, six-month-old SS mice endured 20-min transient hypoxia-ischemia (tHI), but showed enhanced leukocyte and platelet adherence to the cerebral blood vessel, as well as, extensive vascular perfusion deficits and fibrin deposition at 4 h post-injury, followed by greatly increased mortality than AA and AS mice at 24 h recovery (p=0.035). Importantly, intravenous tPA administration at 0.5 h post-tHI markedly improved vascular reperfusion, mitigated fibrin deposition, and cut the mortality of SS mice by 50%. These results indicated that humanized sickle mice develop hyper-coagulation and hypersensitivity to HI-induced stroke without large-vessel obstructive vasculopathy at up to 6 months of age. Elevated resistive index may be an early ultrasonic marker for sickle cell vasculopathy and the risk of SCI in SCA. Future studies are warranted to confirm the therapeutic benefits of thrombolytic stroke therapy in SCA.

Disclosures: **Y. Sun:** None. **J. Lee:** None. **H. Huang:** None. **M.B. Wagner:** None. **C.H. Joiner:** None. **D.R. Archer:** None. **C. Kuan:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.07/W33

Topic: C.08.Stroke

Support: NS094507

Title: Probiotic treatment after transient cerebral ischemia ameliorates long-term cognitive deficits in mice

Authors: *C. POON, M. MURPHY, C. IADECOLA, J. ANRATHER
BMRI, Weill Cornell Med. Col., New York, NY

Abstract: Stroke is the leading preventable cause of long-term disability and interventions for improving stroke outcome are necessary. Studies have shown differences in stroke size and functional outcome with changes in gut microbiota by modulating immune response. Altering intestinal microbiota prior to middle cerebral artery occlusion (MCAO) provides neuroprotection (Benakis, Nat Med, 2016), whereas transplantation of dysbiotic feces increase ischemic brain injury (Singh, JNeurosci, 2016). We investigated whether administration of a probiotic bacterial preparation before or after MCAO would affect infarct size and neurological outcome. *Methods:* Probiotic preparation (5 lactobacilli, 2 bifidobacteria, 1 S. thermophilus) was given at a concentration of 10^9 live bacteria/ml drinking water for 2 weeks prior to MCAO in C57Bl/6 mice (male, 9 wks old). Neurological function and infarct volume was determined 3 days after MCAO. Another group of C57Bl/6 mice (male, 9 wks old) underwent MCAO and received probiotic bacterial preparation via gastric gavage for 5 days post-MCAO then via drinking water up to 2 weeks post-MCAO. Corner test was performed at day 7, tape removal test and novel object recognition task were performed at day 14, followed by determination of stroke volume. Control groups received drinking water containing suspension matrix without bacteria. *Results:* Infarct volumes were not different between mice pretreated with probiotics and control prep (n=6-8/group, $70\pm11 mm^3$ vs $71\pm6 mm^3$, $p>0.05$). Bederson scores were not significantly different between groups (n=6-8/group, $p>0.05$). In mice treated with probiotics for 2 weeks after MCAO, corner test at 7 days showed no differences in sensorimotor recovery among groups (n=10-14/group). Tape test at 14 days showed no significant differences in tape contact time or tape removal time (n=6-9/group, $p>0.05$). Novel object recognition at day 14 showed probiotic treated mice spent significantly more time exploring the novel object compared to control (n=10-14/group, 73 vs 43 % total exploration time, $p<0.001$). Brain tissue loss was not significantly different among groups (n=4, $p>0.05$). *Conclusions:* Probiotic treatment before MCAO did not affect lesion size and neurological outcome. Probiotic treatment after MCAO did not improve sensorimotor function, but ameliorated the memory deficits observed after stroke. Our findings

indicate that probiotics might improve hippocampal function after cerebral ischemia, but mechanisms remain to be elucidated. Nevertheless, our data raise the possibility that probiotic therapies may protect stroke patients from memory impairment and prevent post-stroke dementia.

Disclosures: C. Poon: None. **M. Murphy:** None. **C. Iadecola:** None. **J. Anrather:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.08/W34

Topic: C.08.Stroke

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

Title: Brain metastasis and stroke repair: Analogous cellular interactions and events

Authors: *N. S. THAREJA[1], R. LEE[1], R. PRAKASH[1], I. WITZ[2], S. CARMICHAEL[3]
[1]Neurol., UCLA, Los Angeles, CA; [2]Tel Aviv Univ., Tel Aviv, Israel; [3]UCLA Sch. Med., Los Angeles, CA

Abstract: Cancer and stroke are amongst the leading causes of disability in the United States. There are key phenotypic similarities between stroke tissue repair and brain metastasis. In stroke tissue repair, immature neurons travel long distances and localize to the vasculature in the stroke region, interacting extensively with astrocytes. In brain metastasis, metastatic cells break off from primary tumors, travel within the vasculature to the brain, and interact with astrocytes to establish secondary tumors. Although studies have identified molecules common to both phenomena, little is known about the specific interactions that occur between these two phenomena in the brain.
We examined whether these two phenotypically similar phenomena interact in murine models of ischemic stroke and metastatic melanoma. Distal middle cerebral artery occlusions were performed on immunocompromised NOD-Scid Gamma mice followed by intracardiac injections of human metastatic melanoma 7 days after stroke, when peak neurogenesis occurs. Metastatic cells localized to the peri-infarct region in the stroke cohort but did not localize to the corresponding cortex in control, non-stroke animals. This preferential localization of melanoma cells to the peri-infarct region was not due to hemodynamic changes, as fluospheres injected 7 days after stroke did not preferentially travel to the peri-infarct region. To study a possible effect of differences in blood brain barrier, we stained for albumin using immunohistochemistry and measured the intensity of albumin in the perivascular space. The intensity of extravasated albumin on Day 7 in the stroke cohort did not differ significantly from corresponding controls in the contralateral cortex, confirming that differences in blood brain barrier integrity did not cause

the preferential migration of melanoma.
Our studies confirm that tissue repair after stroke causes the preferential localization of metastatic cells to the peri-infarct region independent of hemodynamic changes or differences in blood brain barrier integrity. Ongoing studies will examine melanoma interactions with cellular components of the regenerative niche and look at molecular similarities between stroke repair and brain metastasis.
Supported by Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF).

Disclosures: N.S. Thareja: None. **R. Lee:** None. **R. Prakash:** None. **I. Witz:** None. **S. Carmichael:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.09/W35

Topic: C.08.Stroke

Title: Stroke induces central nervous system specific T cell responses

Authors: *U. SELVARAJ[1], P. PANDIYAN[2], X. KONG[2], F. MIRÓ[3], X. URRA[3], S. B. ORTEGA[4], E. J. PLAUTZ[5], A. M. PLANAS[7], A. M. STOWE[6]
[1]Dept. of Neurology; Dept. of Immunol., UTSW Med. Ctr., Dallas, TX; [2]UTSW medical center, Dallas, TX; [3]August Pi i Sunyer Biomed. Res. InsVtute, Barcelona, Spain; [5]Neurol. & Neurotherapeutics, [6]Neurol. and Neurotherapeutics, [4]UT Southwestern Med. Ctr., Dallas, TX; [7]Dept Brain Ischemia and Neurodegeneration, IIBB-CSIC IDIBAPS, Barcelona, Spain

Abstract: Introduction: Stroke patients exhibiting increased colocalization of antigen-presenting cells to the neuronal antigens microtubule-associated protein 2 (MAP2) and N-methyl-D-aspartate (NMDA) receptor subunit 2A (GluN2A) in lymph nodes had smaller infarctions at day 7, and better long-term improvement at 3 months. However, patients with poor outcome exhibited more myelin-reactive colocalization. We hypothesized that post-stroke T-cell responses to MAP2 and GluN2A have a neuroprotective profile after focal stroke in mice.
Methods: Male C57BL/6 mice (B6, Jackson Labs, 8-10 wks old) were subjected to 60-min transient middle cerebral artery occlusion. Spleen and cervical lymph nodes were harvested 4, 8 and 10 days post-stroke, stained with CFSE, and cultured with GluN2A and MAP2 peptides for 6 days. Cell cultures were stained with fluorescently-tagged antibodies (TCRβ, CD4, CD19, CD8, CD25, TNF-α, IFN-γ, IL- 10, IL-6, IL-4, IL-17) and quantified by flow cytometry. CD25+/CFSE-low responses were considered positive when ΔPF (test condition[[Unsupported Character - Symbol Font □]]non-stimulated condition) exceeded 1% and stimulation index (SI, test condition/non-stimulated condition) was greater than 2.
Results: Stroke mice had higher CNS-autoreactive T-cells in spleen compared to sham mice

(10/12mice vs 4/7mice). Further, in stroke mice, CD8+T-cells (10/12mice) had higher GluN2A-specific responses in spleen compared to CD4+T-cells (4/12mice). GluN2A-15 peptide-specific CD4+ (17% and 4%) and CD8+ (35% and 22%) splenic T-cells primarily produced pro-inflammatory cytokines TNF-α and IFN-γ, respectively. Animals with lower infarct volumes had higher number of IL-10- and TNF-α- producing neuronal antigen-specific CD4 and CD8 T-cells in spleen.
Conclusion: CNS-derived antigens induce autoimmune responses as early as four days after stroke in outbred mice. We now identified GluN2A and MAP2 peptides that elicit strong positive responses from the CD4+ and CD8+ T-cells at 8 and 10 days post-stroke in B6 mice. Future experiments will determine cytokine profile of neuronal antigen-specific cells in brain and establish if they are protective after stroke using *in-vitro* and *in-vivo* models.

Disclosures: U. Selvaraj: None. **P. Pandiyan:** None. **X. Kong:** None. **F. Miró:** None. **X. Urra:** None. **S.B. Ortega:** None. **E.J. Plautz:** None. **A.M. Planas:** None. **A.M. Stowe:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.10/W36

Topic: C.08.Stroke

Support: Research Project for Practical Applications of Regenerative Medicine from Japan Agency for Medical Research and Development

Title: Autologous bone marrow stromal cell transplantation against stroke; rainbow trials

Authors: *H. SHICHINOHE, M. KAWABORI, K. HOUKIN
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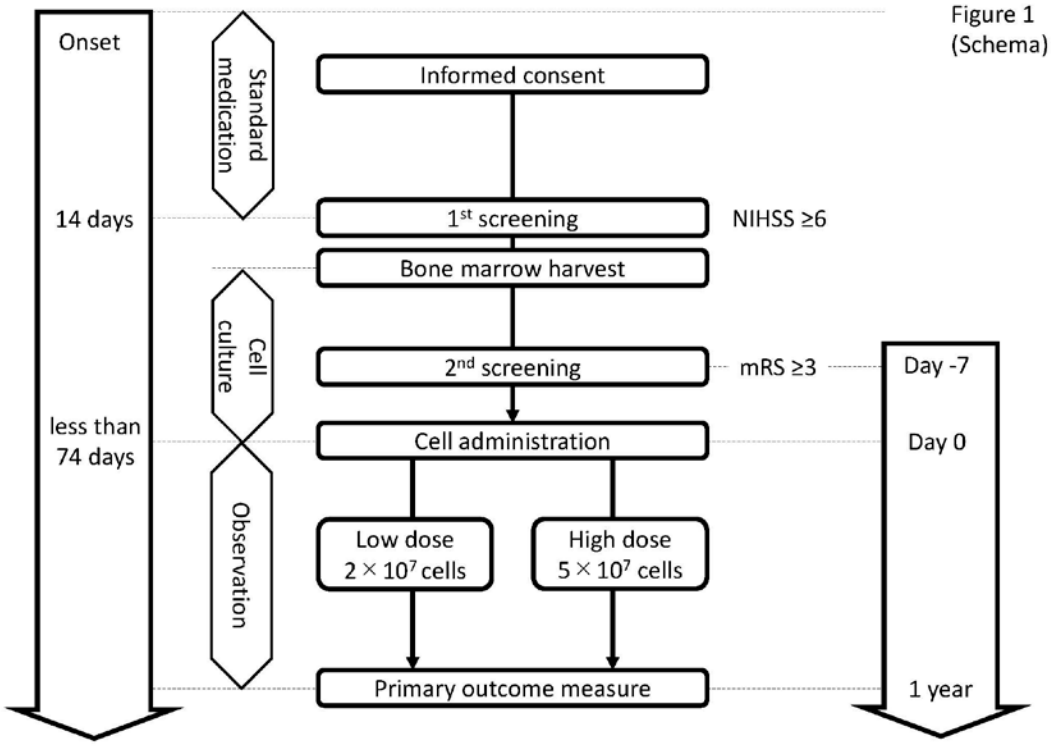
Abstract: Recent studies have elucidated that the bone marrow stromal cells (BMSCs) have therapeutic potential against stroke. Now we prepare the novel clinical trials, Research on advanced intervention using novel bone marrow stem cell (RAINBOW) study. It is a phase 1, open label, uncontrolled, dose response study. The primary purpose is to determine the safety of autologous BMSC product, HUNS001-01, when administered to acute ischemic stroke patients. After 2 weeks pass from the onset, about 50 mL of bone marrow is extracted from the iliac bone of the patient. The BMSCs are cultured with human platelet lysate (hPL) instead of fetal calf serum (FCS). They are labeled with superparamagnetic iron oxide (SPIO). HUNS001-01 is administered around the infarct area stereotactically. Each patient will be given a dose of 20 or 50 million cells. Neurological scoring, MRI for cell tracking, 18F-FDG PET, and 123I-Iomazenil SPECT were performed for 1 year after the administration. Estimated enrollment is more than 6

patients. The trials will start in this winter. In conclusion, it is expected to clarify the therapeutic mechanism of autologous BMSC transplantation.



	Screening			Follow up								
	1st screening	BM hervest	2nd screening	Pre-administration	Post-administration							
	Onset to14 days		Day -7 (±1)	Day 0		Day 1	Day 3	Day 7	Day 14	Day 30 (±3)	Day 90 (±30)	Day 180 (±30)	Day 360 (±30)
Informed consent	X												
Medical history	X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height	X												
Serological tests	X		X		X	X	X	X	X	X	X	X	X
Biochemical tests	X		X		X	X	X	X	X	X	X	X	X
Urinalysis	X		X							X	X	X	X
Urine hCG-β (If needed)	X									X	X	X	X
Infectious disease inspection	X												
12-lead electrocardiogram	X		X			X		X		X	X		X
Chest X-ray examination	X		X			X		X		X	X		X
Neurological examination	X		X			X		X		X	X	X	X
MRI	X		X	X	X		X	X	X	X	X	X	X
FDG-PET and IMZ-SPECT			X							X	X		X
Bone marrow harvest		X											
Cell product administration				X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X

Disclosures: H. Shichinohe: None. **M. Kawabori:** None. **K. Houkin:** None.

Poster

051. Stroke: Role of Non-Neuronal Cells and Other Factors in Pathogenesis

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 051.11/X1

Topic: C.08.Stroke

Support: Supported by Addis Ababa University, College of Health Sciences, Post-graduate Medical School

Title: The predictors of mortality from acute stroke in patients admitted to a hospital: The clinical, laboratory and imaging profile analysis

Authors: *Y. D. GELAN, A. A. WELDEAB
Neurol., Addis Ababa University, Col. of Hlth. Sci., Addis Ababa (Gpo), Ethiopia

Abstract: Background
Stoke is the second most common cause of death. Recent studies in Africa have shown an alarming rise of mortality due to stroke. The main objective of this study was to determine the predictors of inpatient mortality of stroke among patients who were admitted to Addis Ababa University, Tikur Anbessa Specialized Teaching Hospital.
Methods
We conducted a review of clinical data registry of 227 patients admitted with the diagnosis of acute stroke based on World Health Organization definition from July 1, 2013 to June 30, 2016. The diagnosis of stroke was confirmed by brain imaging. We collected the socio-demographic information, detailed clinical presentation, laboratory results, imaging profiles and outcome on discharge from patient's medical records. Univariate statistical analysis and multiple binary logistic regressions were done to identify independent predictors of mortality.
Results
Out of 227 admitted patients, 113(49.8%), 11(48.9%), 3(1.3%) had ischemic stroke, hemorrhagic stroke and cerebral venous thrombosis respectively. Hypertension was the most common risk factor (52%) followed by cardiac diseases (22.5%). Sixty-eight patients died within the hospital making the case fatality rate of 30%. The case fatality rate is higher in hemorrhagic stroke than ischemic stroke (37.8% vs. 23%, P=0.016). Advanced age and female sex were not associated with increased mortality. The following factors were significantly associated with high mortality on univariate analysis: hypertension (OR=2.106 (1.17-3.79)), fever (OR=14.29 (6.57-31.09)), shock (OR=10.04 (2.70-37.27)), oxygen desaturation (OR=8.824, (4.63-16.81)), Glasgow coma scale ≤ 8 on initial evaluation (OR=3.722 (1.76-7.88)), swallowing difficulty (OR=9.536 (4.28-21.25)), incontinence (OR=3.382 (1.84-6.22)), speech and language disturbances (OR=4.357 (1.87-10.18)), aspiration pneumonia (OR=7.49 (3.94-14.25)), renal failure in the hospital (OR=2.19 (1.16-4.17)), delirium (OR=1.459 (1.33-1.60)), raised baseline creatinine (OR=4.128

(2.00-8.50)), leukocytosis (OR=1.95 (1.09-3.50)), and subfalcian or uncal herniation (OR=4.045 (1.57-10.41)).
Independent predictors of inpatient mortality from stroke were development of hypotension, oxygen desaturation and fever in the hospital, and presence of subfalcian and/or uncal herniation on brain imaging.

Conclusion

Case fatality is very high in our hospital. The hemodynamic derangements and infectious complications are significant predictors of mortality in our patients which signifies the need for establishment of stroke unit where intensive monitoring of patients and new therapeutics will be delivered.

Disclosures: Y.D. Gelan: None. **A.A. Weldeab:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.01/X2

Topic: C.08.Stroke

Support: NIH Grant R15 HD075166-01A1

NIH Grant R21 HD088783-01

The Catholic University of America Dissertation Grant

Title: Initial kinematic evaluation of a spring powered arm exoskeleton for stroke rehabilitation

Authors: *J. CHEN[1], P. LUM[2]
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Abstract: This study aims to develop a spring-operated wearable enhancer for arm neurorehabilitation (“SpringWear”) that provides partial arm gravity support, elbow extension assistance and forearm supination assistance. Exoskeletons of this type can improve kinematics, reduce effort and reduce fatigue during repetitive task practice interventions for neurorehabilitation. Chronic stroke patients performed a number of tasks with and without assistance from the SpringWear, and the kinematics of the movements were compared. Tasks included 4 range of motion (ROM) tests and 3 functional tasks in two conditions. In the “unassisted” condition, no assistance to movement was provided, but elastic cords were attached at the shoulder flexion degree-of-freedom (DOF) to remove the effect of gravity on the device only. In the “assisted” condition, springs were added until the subject could hold the shoulder at 90 degrees of flexion, extend the elbow to near full extension, and supinate the forearm to near

full supination. For the final 2 subjects, a third condition was performed whereby the springs at the shoulder DOF was added to provide approximately 100% gravity compensation. All thirteen subjects had immediate gains in assisted DOFs during ROM tasks. With assistance from SpringWear, subjects had significant gains in maximum shoulder flexion (gain= 27.6±17.8 degrees; $p<0.001$), elbow extension (gain= 18.7±13.2 degrees; $p<0.001$), and forearm pronation supination (gain= 38.8±32.2 degrees; $p=0.001$), and also had significant ROM gains in elbow flexion/extension (gain= 16.9±10.0 degrees; $p<0.001$). Index finger PIP extension increased significantly with SpringWear assistance (gain= 16.2 ± 20.3 degrees; $p = 0.033$). Subjects had significant gains in maximum shoulder flexion ($p<0.001$), elbow extension ($p=0.002$) and forearm pronation/supination ($p<0.001$) with assistance from SpringWear during functional tasks. The forward reach workspace also increased significantly with assistance (gain= 8.2±7.4 cm; $p=0.002$). In the two subjects tested with 100% arm gravity support, index finger extension was further improved. The total index finger extension angle, defined as the sum of the angles of the MCP, PIP and DIP, increased by 44.3 and 65.0 degrees in these two subjects. No consistent improvement in the ability to complete functional tasks was noted. This was likely due to only small improvements in hand movement with SpringWear proximal assistance. Use of a hand device with SpringWear may yield better results during functional task practice and help overcome the problem of abnormal synergies linking distal activation of flexor muscles when lifting the arm against gravity.

Disclosures: J. Chen: None. **P. Lum:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.02/X3

Topic: C.08.Stroke

Support: NIH,NINDS NS42617

NIH,NINDS NS085272

AHA 12SDG11780023

Title: A standardized robot-assisted mechanical therapy (RAMT) approach to stroke rehabilitation

Authors: *M. BALCH[1,2], S. KHANNA[1], H. HARRIS[1], S. GNYAWALI[1], C. K. SEN[1], C. RINK[1]
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Abstract: Nearly 1,000 randomized clinical trials in stroke rehabilitation over the past thirty years have tested a range of neurorehabilitation techniques that include repetitive task training, biofeedback, constraint-induced movement, robotics, and virtual reality. Despite these efforts, systematic reviews of widely used neurophysiological approaches in stroke have reported mixed outcomes and evidence suggesting no superiority for one approach over another. Pre-clinical rehabilitative study is limited, mechanisms are not fully understood, and research less-commonly focuses on the stroke-affected periphery. This work addresses our development of Robot-Assisted Mechanical Therapy (RAMT) for objective study of post-stroke manual therapy.
Male Wistar rats (aged 10 weeks) were subjected to middle cerebral artery occlusion (MCAO), after which they received either 30 minutes of RAMT treatment daily under anesthesia over the medial stroke-affected hindlimb, or no treatment (anesthesia only). Treatment was applied at 0.5N force with 1Hz frequency in a 10mm linear pattern beginning post-stroke day (PSD) 1 and continuing to PSD3, PSD7, or PSD 14. Muscle perfusion, gait, and sensorimotor behavior were tested, and mechanosensitive targets of stroke and RAMT were queried. To facilitate further pathophysiological investigation, protocols were developed to apply hindlimb MRI for atrophy study, myosin ATPase staining for skeletal fiber type analysis, and immunostaining for neuromuscular junction morphology and inflammatory cell infiltration.
Compared to untreated controls, RAMT-treated rats benefited from higher perfusion in the medial stroke-affected hindlimb and superior post-stroke gait and sensorimotor behavior. RAMT protected from post-stroke induction of myostatin (a negative regulator of skeletal muscle growth) and IP-10/CXCL10 (a pro-inflammatory mediator) while upregulating expression of anti-inflammatory IL-1ra. RAMT also promoted greater infiltration of anti-inflammatory M2 macrophages in affected muscle.
Taken together, RAMT enables reproducible, objective, pre-clinical study of post-stroke manual therapy. We identify that stroke pathophysiology extends beyond the CNS to affect signal transduction and inflammatory response in paretic muscle. Ongoing efforts seek to characterize skeletal muscle pathophysiology after stroke through analysis of fiber type, neuromuscular junction morphology, atrophy, and inflammatory cell profiling.

Disclosures: M. Balch: None. **S. Khanna:** None. **H. Harris:** None. **S. Gnyawali:** None. **C.K. Sen:** None. **C. Rink:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

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Program#/Poster#: 052.03/X4

Topic: C.08.Stroke

Support: DFG RE 2740/3-1

Title: Effects of non-invasive brain stimulation on motor learning, motor recovery and long term performance after rodent stroke

Authors: *B. FRITSCH, F. ROTH, J. REIS
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Abstract: Stroke is the leading cause of lasting motor disability. Therefore augmentation of recovery is needed. Due to its capability to transiently modulate cortical excitability and to improve cognitive function and motor learning tDCS is a cheap and well tolerated tool to improve motor rehabiltation. However, for successful translation in clinical routine fundamental research is required.
Here we investigate differences of tDCS and tRNS on stroke volume and spontaneous recovery as well as the effects of anodal tDCS on re-learning of a motor task after stroke.
Both stimulation paradigms did not affect the stroke volume, while leaving the spontaneous recovery, measured by a neurological scale including motor function, unaffected. Stroke induced a comparable deficit a previously learned motor task. atDCS improved re-learning of the task without generalization to other motor functions.

Disclosures: **B. Fritsch:** None. **F. Roth:** None. **J. Reis:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

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Program#/Poster#: 052.04/X5

Topic: C.08.Stroke

Support: NIH Grant 1R21NS088818

Title: The relationship between motor unit firing rates and the hyperemic response to exercise post stroke

Authors: *S. A. MURPHY[1], M. DURAND[3], F. NEGRO[4], B. D. SCHMIT[5], A. S. HYNGSTROM[2]
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Abstract: The purpose of this study was to quantify the relationship between blood flow and motor unit firing rates in exercising muscle post stroke. A high density (64 channel, OT Bioelettronica) sEMG was used to record and extract single motor unit firing rates in the vastus lateralis muscle of 8 individuals with chronic stroke (60.0 ± 1.3 yrs old) and 4 individuals without stroke (62.0 ± 2.3 yrs old) during isometric knee extension contractions. Each subject

performed contractions at 20, 40, 60, and 80 % of their maximal voluntary contraction (MVC) for 10 seconds. Immediately after each contraction, blood flow measurements were taken using ultrasound over the femoral artery. Motor unit firing rates increased with intensity while there was a blunted response in motor unit firing rates in paretic motor units as intensity increased. Mean firing rates for stroke were on average lower compared to control firing rates at 20% (7.8 ± 1.7 pps vs. 9.0 ± 1.7 pps), 40% (8.2 ± 1.7 pps vs 10.0 ± 1.5 pps), 60% (8.4 ± 2.4 pps vs. 11.7 ± 1.7 pps), and 80% (8.4 ± 2.3 pps vs. 11.6 ± 1.6 pps) MVC. On average, the hyperemic response to exercise for stroke was also lower compared to control at 20% (181 ± 166 ml/min vs. 241 ± 60 ml/min), 40% (204 ± 117 ml/min vs 394 ± 102 ml/min), 60% (264 ± 191 ml/min vs. 503 ± 225 ml/min), and 80% (321 ± 211 ml/min vs. 493 ± 203 ml/min) MVC. Stroke motor unit firing rates had a blunted response with increased blood flow compared to control motor units. Motor unit firing rates were correlated with the hyperemic response with a stroke slope value of 0.004 pps/ml/min ($R^2 = 0.78$) compared to the control slope value of 0.01 pps/ml/min ($R^2 = 0.95$). These results suggest that a blunted hyperemic response to exercise may be present post stroke and is related to impaired modulation of motor unit firing rates.

Disclosures: S.A. Murphy: None. **M. Durand:** None. **F. Negro:** None. **B.D. Schmit:** None. **A.S. Hyngstrom:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: HHS grant 90IF0090-01-00

NICHD 2RO1HD039343

Title: Altered effective EEG connectivity between sensorimotor cortices following an EMG-driven FES-assisted task-specific arm/hand intervention in moderate to severe chronic stroke

Authors: *K. B. WILKINS[1], J. P. DEWALD[2], J. YAO[3]
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Abstract: Introduction: Previous evidence shows that contralesional cortical activity increases as a function of shoulder abduction loading in individuals with stroke, and is associated with greater impairment. Additionally, these individuals demonstrate altered fMRI resting state and task-related connectivity between ipsilesional and contralesional primary motor cortices, which may contribute to the observed increased contralesional activity. In this study, we investigated

intervention-induced changes in sensorimotor cortical activity and connectivity related to hand control in individuals with moderate to severe chronic stroke.
Methods: Eight moderate to severe (upper extremity Fügl Meyer < 30) chronic stroke individuals participated in a 7-week task-specific intervention, assisted by an electromyography-driven functional electrical stimulation device for 3 visits/week. Cortical activity related to hand opening with or without lifting was measured using High-Density EEG (HD-EEG). Additionally, we quantified HD-EEG task-related effective connectivity for both tasks within a motor network consisting of primary motor cortex (M1), premotor cortex (PM), and supplementary motor area (SMA) using dynamic causal modeling for induced responses.
Results: Subjects demonstrated an intervention-induced shift in cortical activity from the contralesional to the ipsilesional hemisphere during paretic hand opening both with and without lifting. This shift was driven by a decrease in activity in contralesional primary sensorimotor cortex for hand opening, and an increase in activity in ipsilesional primary sensorimotor cortex for simultaneous lifting and opening. Dynamic causal modeling showed intervention-induced decreases in task-related connectivity from ipsilesional M1 to contralesional M1 (γ-γ) during hand opening, and changes in intrinsic connectivity within ipsilesional M1 (γ-β) during opening while lifting. The combination of changes in cortical activity and oscillatory connectivity suggests an intervention-induced cortical reorganization involving increased reliance on ipsilesional sensorimotor cortex and decreased reliance on contralesional sensorimotor cortex related to hand/arm control.

Disclosures: **K.B. Wilkins:** None. **J.P. Dewald:** None. **J. Yao:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.06/X7

Topic: C.08.Stroke

Title: A computational model of exercise-based recovery from unilateral spatial neglect

Authors: G. SEDDA[1], M. OTTONELLO[2], E. FIABANE[2], A. SEDDA[3], C. PISTARINI[2], *V. SANGUINETI[1]
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Abstract: Unilateral spatial neglect is a common disabling condition following stroke, particularly after right hemisphere damage. This neuropsychological disorder is characterized by a failure to report, orient toward, or respond to stimuli in contralesional space, which cannot be attributed to primary motor or sensory dysfunction.. The related symptoms differ from subject to subject, and the underlying mechanisms are poorly described. Prism adaptation is considered an

effective treatment, but new strategies based on virtual reality have been recently developed for assessment and rehabilitation of neglect. In the last few years, some attempts have been made to relate the neglect symptoms, the related cortical lesions, and the effects of the rehabilitation approaches through neural models. However, their predictions are purely qualitative and do not allow to explain individual behaviours. Here we describe the trial-by-trial dynamics of training-induced recovery from neglect in terms of state-space dynamical models - an approach that is largely used to study sensorimotor adaptation. Based on previous evidence from empirical findings and neural models, we model neglect as an altered cortical representation of visual stimuli located within the left hemispace. The model assumes that the mismatch between such representation and the corresponding hand positions is the driving force of the recovery process. We show that the model qualitatively reproduces empirical observations in prism adaptation experiments - decrease of neglect symptoms after right prism adaptation, no effect or worsening of symptoms after adaptation to left prims. Further, we used the same model to analyse the temporal evolution of performance in a rehabilitation trial based on reaching movements within an adaptive virtual reality environment. We used standard system identification techniques to fit the model to time series data from the rehabilitation trial. The modeling framework allows to quantitatively interpret individual subject data, facilitates interpretation of rehabilitation training and may suggest optimal forms of treatment.

Disclosures: G. Sedda: None. **M. Ottonello:** None. **E. Fiabane:** None. **A. Sedda:** None. **C. Pistarini:** None. **V. Sanguineti:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: NIH R01 NS053813

T32 EB009406

Title: The time required to plan ballistic elbow movements is unaffected by stroke

Authors: *R. L. HECKMAN[1], E. J. PERREAULT[2]
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Abstract: Impairments in voluntary reaching significantly reduce quality of life following stroke. While impairments in movement initiation and execution are well-documented, little is known about the contributions of motor planning. Deficits in motor planning may contribute to impairments in voluntary reaching if greater time is required to prepare a motor plan. EEG-based

cortical measures suggest planning requires more time post stroke, but these measures are indirect. Startle-evoked movements, an alternate method for investigating motor planning, more directly link to the motor action resulting from a plan. Studies that have shown motor planning is intact following stroke allowed ample time for motor planning. The objective of this work was to constrain the time allowed for planning below the 2.5 seconds EEG-based studies suggest is required. We tested the hypothesis that stroke subjects would require longer times to plan a movement than age-matched controls.
Data were collected from 9 stroke subjects (45-76 years old, 4 females) with mild to severe impairment (11-51/66) on the Upper Extremity domain of the Fugl-Meyer Assessment and 10 age-matched controls (41-73 years old, 6 females). Subjects were instructed to make ballistic elbow movements in either flexion or extension. The time available to plan a movement was varied by changing the certainty of the movement target position and the time between target presentation and the cue to move. Target certainty was fixed in extension or varied between flexion and extension. Target presentation time was either 1.5 or 3.0 seconds before the cue to move. Loud acoustic stimuli were used to startle subjects during extension movements and evoke an early release of the available movement plan. Sternocleidomastoid (SCM) muscle activity was used as an independent marker of startle. Movement kinematics and electromyograms were used to quantify the state of the motor plan at the time of startle.
The probability of eliciting a SCM response was 0.64 +/- 0.34. The onset of extensor muscle activity in the presence of SCM activity was 95+/-25 ms. There were no significant effects of subject group, target certainty or target presentation time for probability of SCM ($p>0.5$) or onset time ($p>0.3$). Extension movements were significantly decreased post stroke ($p<0.001$), but there were no effects of target certainty or presentation time ($p>0.5$). These results suggest varying the time available to plan a movement, either by changing certainty of the target position or time between target presentation and the cue to move, does not affect the state of the prepared motor plan. Stroke subjects do not require longer times to plan ballistic elbow movements.

Disclosures: R.L. Heckman: None. **E.J. Perreault:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: AHA Grant: 16GRNT31010001

Title: Intensive non-paretic arm training in chronic stroke patients with severe paresis improves functional independence without compromising paretic arm function

Authors: *C. MAENZA[1,2], R. VARGHESE[4], D. C. GOOD[5], C. J. WINSTEIN[4], D. A. WAGSTAFF[3], R. SAINBURG[1,2]
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Abstract: We previously demonstrated functionally limiting hemisphere specific motor deficits in the non-paretic, ipsilesional arm of chronic stroke patients. In a small pilot study in patients with severe paresis, we showed that non-paretic arm deficits can improve with non-paretic arm training. We now extend this study to a larger two-track cross-over design that includes both non-paretic arm training and sham-training. We ask whether non-paretic arm training can improve functional independence, without detriment to the paretic arm, and we explore the durability of these effects. This report includes only one track of our study, for which we have thus far collected data in stroke survivors with moderate to severe paresis over a 12-week interval with 5 testing sessions that assessed non-paretic arm function, functional independence, and paretic arm impairment. After the initial test (Test 1), participants were retested (Test 2) after 3-weeks to confirm stability in baseline performance. During the following 3 weeks, participants engaged in intense ipsilesional arm training for three 1.5-hour sessions per week. During training, patients engaged in virtual reality (VR) games that required rapid and accurate motions of the non-paretic arm for 45 minutes. Following VR activities, the patients engaged in real-life activities involving resistive exercise, and challenging use of the non-paretic arm. After a post-test (Test 3), participants engaged in 3 weeks of sham training involving playing computer and board games to control for non-specific effects. They were again tested following the sham training (Test 4), and again after 3 weeks to assess durability of training (Test 5). For the non-paretic arm, our primary dependent measures were: 1) Jebsen-Taylor Hand Function Test (JTHFT), 2) The motor subscale of the Functional Independence Measure (FIM), and 3) Hand dynamometry. For the paretic arm, our primary dependent measure was the Fugl-Meyer Assessment. Our preliminary results indicate substantial improvements in response to non-paretic arm training in non-paretic arm performance (JTHFT) and functional independence (FIM), but not in general strength (dynamometry). This suggests that improvements were in coordination. Importantly, the paretic arm showed a modest, but significant reduction in impairment. Our results suggest that training of the ipsilesional arm in stroke survivors can improve non-paretic arm performance, which generalizes to improve functional independence. These improvements are durable over time, and this training is not detrimental to paretic arm function, and may slightly decrease paretic arm impairment.

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Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: Grant-in-Aid for Scientific Research from the Niigata University of Health and Welfare H28C14

Japan Society for the Promotion of Science, Grant-in-Aid for Scientific Research 16K16445

Title: Effect of early and late treadmill exercise on motor functional recovery and cerebral cortex after hemorrhage in rats

Authors: *K. TAMAKOSHI[1], K. ISHIDA[2], K. HAYAO[1], H. TAKAHASHI[1], H. TAMAKI[1]
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Abstract: Early rehabilitation after stroke is routinely performed in many rehabilitation institutions. Previously, early rehabilitation has been demonstrated to have positive effects; however, detailed mechanisms mediating these effects remain unclear. The present study focused on the effect of early and late treadmill training on motor functional recovery, lesion volume, and cortical damage following intracerebral hemorrhage (ICH) in rats. ICH was induced in rats by an injection of collagenase into the left striatum. They were randomly divided into four groups: no training ICH (ICH, n = 9), no training placebo surgery (SHAM, n = 8), early treadmill training (ICH + ET, n = 6), and late treadmill training (ICH + LT, n = 7) groups. The ICH + ET group was trained for 7 days from the 2nd to 8th day after the surgery. The ICH + LT group was trained for 7 days from the 9th to 15th day after the surgery. The sensorimotor function was assessed using forelimb placing and the horizontal ladder test. The lesion volume, cortical thickness, and number of neuronal cells were analyzed using Nissl staining. The ICH + ET group showed a significantly improved sensorimotor function compared with the ICH group. The cortical thickness and number of neuronal cells in the ICH + ET group were significantly higher than those in the ICH and ICH + LT groups. These results suggest that after a cerebral hemorrhage, compared with late treadmill training, early treadmill training may promote sensorimotor functional recovery by preventing cortical atrophy and cell death in the sensorimotor cortex. Thus, we conclude that early treadmill training following ICH has neuroprotective effects. This work was supported by a Grant-in-Aid for Scientific Research from the Niigata University of Health and Welfare (H28C14) and a Japan Society for the Promotion of Science, Grant-in-Aid for Scientific Research (16K16445). I have no financial relationships to disclose.

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Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.10/X11

Topic: C.08.Stroke

Support: NIH Grant R01HD053727

Title: Deficits in proprioception differentially impair arm stabilization and movement after stroke

Authors: ***M. BENGTSON**[1], L. A. MROTEK[2,4], T. STOECKMANN[3], C. P. GHEZ[5], R. A. SCHEIDT[2,6]
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Abstract: Within deliberate actions such as reaching for an object, spatial plans for moving the arm are distinct from those for holding it still. We hypothesized that deficits in coordinating limb stabilization and movement contribute significantly to motor impairments and deficits of motor function after stroke. Eleven neurologically-intact control (C) participants and 10 survivors of stroke (S) underwent both blocked- and mixed-practice training prior to testing on 6 tasks comprised of stabilization and movement actions performed in isolation and sequential combination. During stabilization, participants were to hold the handle of a 1 DOF robot still at a neutral elbow angle for 7 seconds against small, 3 Nm sum-of-sinusoid perturbations. To do so, they were provided visual feedback on a vertical screen consisting of a cursor and a 1.2° target within which to keep the cursor. During the movement task, participants were to make a 30° elbow flexion as quickly and accurately as possible; the cursor was visible at the beginning and end of movement, but was blanked within the middle 20° of the task space. An opaque screen blocked direct view of the arm. Sequential task combinations were designed to determine how stabilization and movement control actions might interact and how stroke might change that interaction. On a day separate from testing, S underwent a battery of clinical evaluations to assess physical, sensory, and cognitive deficits. S showed greater positional variability than C when holding the arm against perturbing forces. When reaching, movements were slower and more segmented in S vs C, whose movements were executed in single strokes. Interactions between stabilization and movement were examined by contrasting performances in sequential tasks to those performed in isolation; sequential performance of stabilization and movement degraded performance of both actions in S but not C. Analysis of electromyographic data from

elbow flexors and extensors in S support the primary hypothesis. Kinematic performances were also more variable in S than C. Regression analysis explored relations between performance and clinical scores in order to explain this variability. Of all clinical tests, only proprioceptive impairment correlated with task performance: S with intact proprioception (S+) had less position variability during arm stabilization compared to S with impaired proprioception (S-). Surprisingly, peak velocities were lower and more submovements were required to reach the target in S+ as compared to S-, suggesting that stroke-related deficits of proprioception can differentially impair the ability to move and to hold the arm still. Support: NIH R01HD053727.

Disclosures: M. Bengtson: None. **L.A. Mrotek:** None. **T. Stoeckmann:** None. **C.P. Ghez:** None. **R.A. Scheidt:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Program#/Poster#: 052.11/X12

Topic: C.08.Stroke

Support: American Heart Association Postdoctoral Fellowship 15POST25680020

Title: Post-stroke limb conditioning converts peripheral monocyte/macrophage subset and enhances long-term recovery

Authors: J. YANG, C. BELTRAN, *S. CHO
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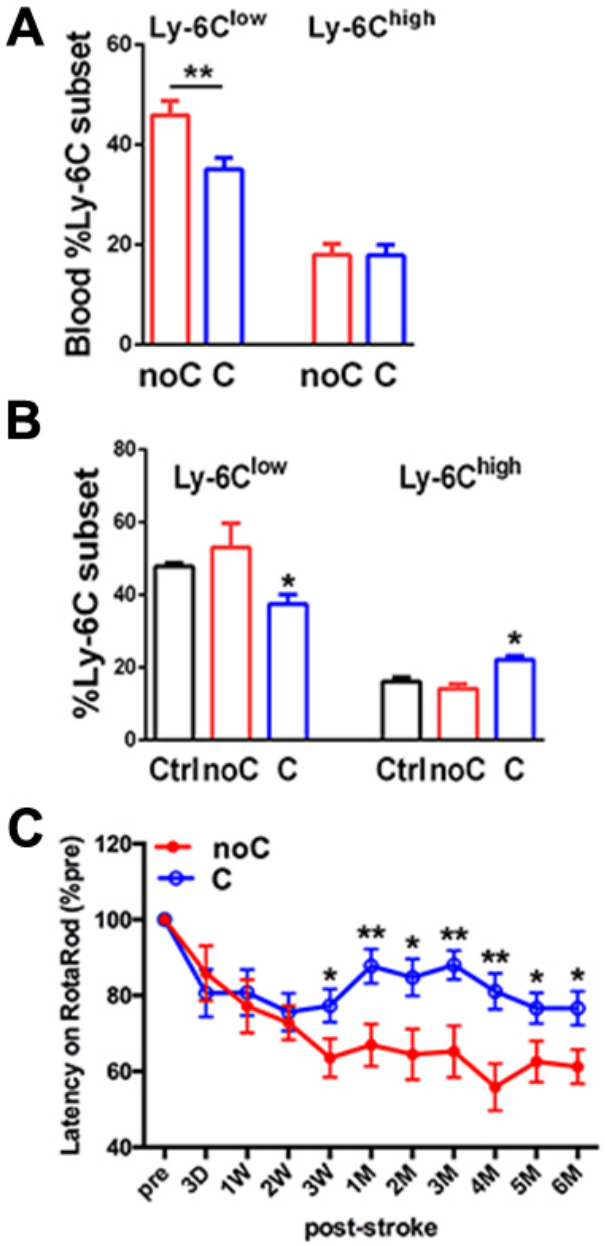
Abstract: Post-stroke limb conditioning (PSLC) has been shown protective effect in pre-clinical and clinical studies. However, protective mechanism underlying the benefit has not been studied. This study investigated whether monocyte/macrophage (MM) subset conversion is an underlying mechanism of PSLC-induced benefit. C57BL/6 male mice (12-week-old) were subjected to transient middle cerebral artery occlusion (MCAO) for 30 min. PSLC was induced 2 h after MCAO by applying 5 cycles of 5 min inflation and 5 min deflation with a cuff on left hind limb. Acute stroke outcome was measures at 3D. Mononuclear cells were isolated from the spleen, blood and brain at 3D and analyzed by flow cytometer. MM conversion test was performed *in vitro* by treating sham-conditioned or PSLC serum to naïve spleen cells. Motor and gait functions were assessed up to 6-month using Rotarod and Catwalk. Acute stroke outcome (injury size) was similar between the two groups at 3D. There was significantly decreased anti-inflammatory (Ly-6C^{low}) subset in the blood without changing pro-inflammatory (Ly-6C^{high}) subset after PSLC (Fig.A). In the stroked brain, PSLC similarly decreased Ly-6C^{low} subset ($p< 0.001$) and showed increased Ly-6C^{high} subset ($p<0.05$). Spleen MM showed no changes. Compared to sham-conditioning serum-treated cells, those with PSLC serum resulted Ly-6C^{low}

reduction and Ly-6C^{high} increase, suggesting PSLC converted anti- to pro-inflammatory MMs (Fig.B). Mice with PSLC showed enhanced motor and gait functions during a recovery phase (Fig.C). The study showed PSLC induces peripheral monocyte conversion from anti- to pro-inflammatory subsets and the changes is associated with functional recovery without affecting acute outcome. The conversion from anti- to pro-inflammatory subset may provide more immunocompetent MMs in periphery during critical acute-stroke period and lead to enhanced functional recovery. This study provides a potential application of PSLC as a neuroimmune-based strategy for patients with ischemic stroke.



Disclosures: **J. Yang:** None. **C. Beltran:** None. **S. Cho:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: TOYOTA Motor Corporation Grant

Title: Electroencephalogram phase synchrony reflects the clinical status of the post stroke aphasia

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Abstract: Objective: Neural network functions are affected by the focal brain damage due to stroke. We have reported that the EEG phase synchrony indices (PSIs) between the specific electrodes shows significant correlations with the degrees of neurological deficits, such as the unilateral spatial neglect and the upper limb motor impairments in postacute stroke patients. The aim of the current study is to investigate the association between the PSIs of the inferior frontal lobes and the naming ability in the aphasic patients.
Methods: Twenty-two first stroke patients presenting aphasia (mean age ± SD: 68.9 ± 15.6, mean post-stroke days ± SD: 38.0 ± 11.8) with left hemisphere ischemic lesions were enrolled. Age-matched 24 healthy volunteers were recruited as a control group. All subjects or their surrogates signed written informed consent. Patients were assessed using the naming item (full score: 20) of the Standard Language Test of Aphasia (SLTA). We obtained 2.5 minutes of eye-closed EEG signals according to the international 10-20 system. And we computed the interhemispheric PSIs between inferior frontal lobes (F7F8-PSIs), as well as the intrahemispheric PSIs between front-temporal lobes of the ipsilesional (F7T5-PSIs) and contralesional (F8T6-PSIs) hemispheres. The PSIs were computed in five frequency bands including delta (δ), theta (θ), alpha (α), beta 1 (β1), and beta 2 (β2). We compared the PSI values between the patients and the control subjects, and then we evaluated the correlations between the PSIs and the naming ability. For the statistical analysis, Spearman's rank correlation analysis with Bonferroni correction was used.
Results: The F7F8-PSIs of patients were significantly lower than control subjects in the β1 and β2 bands. The F7F8-PSIs significantly positively correlated with the naming scores in the β1

band (p = 0.035). In contrast, The F7T5- and F8T6-PSIs of patients were significantly higher than control subjects in the β2 band (F7T5), and in the δ and θ bands (F8T6). The F7T5-PSIs negatively correlated with the naming scores in the β1 (p = 0.025) and β2 bands (p = 0.020). The F8T6-PSIs negatively correlated with the naming scores in the δ band (p = 0.005).
Conclusion: The PSIs between the inferior frontal lobes and their related areas correlated with the naming scores in the specific frequency bands. Interestingly, contralesional intrahemispheric PSIs also significantly correlated with the naming scores. Elevated intrahemispheric PSIs suggested adaptive roles of the bilateral front-temporal networks in verbal expression of aphasic patients with postacute stroke.

Disclosures: **T. Kawano:** None. **N. Hattori:** None. **Y. Uno:** None. **M. Hatakenaka:** None. **H. Yagura:** None. **H. Fujimoto:** None. **T. Yoshioka:** None. **M. Nagasako:** None. **H. Otomune:** None. **K. Kitajo:** None. **I. Miyai:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.13/X14

Topic: C.08.Stroke

Support: NIH grant KO1- HD059983

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Title: Early virtual reality based hand training post stroke elicits better than expected outcomes

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Abstract: Decreased upper extremity function post-stroke has a substantial negative impact on quality of life. Thus it is critical to develop effective upper extremity rehabilitation interventions that can exceed expected outcomes. One predictive algorithm that utilizes the presence of distal upper extremity motor evoked potentials (MEPs) and active finger extension and shoulder abduction (SAFE score) is the Predicted Recovery Potential algorithm 2 (PREP2) (Stinear et al., SFN 2016). Data from 11 subjects recruited for a more expansive pilot study was collected for sub-analysis to determine whether early and intense hand-focused virtual reality and robotic

training could improve expected upper extremity function. Subjects (mean age, 58 years) were < 30 days post first time stroke and had moderate to severe hemiparesis (UEFMA range, 2-44). All subjects received eight 1-hour sessions of hand-focused training in addition to standard acute rehabilitation. MEPs from the affected first dorsal interosseous muscle and SAFE scores (excluding corticospinal tract lesion load) were obtained at baseline (5-29 days). Clinical outcomes obtained at baseline, post training, and 6 months later included the UEFMA and Action Research Arm Test (ARAT). Subjects were categorized into either an MEP negative group (N=7, never regained MEPs) or a convert group (N=4, MEPs regained after training). Data on the PREP2 algorithm predicts that people with SAFE scores <5 (within 72 hours of stroke) and without MEPs at two weeks post-stroke will have limited to poor upper extremity functional outcomes (ARAT score <32) at 3 months post-stroke. Ten of our 11 subjects met these criteria and of interest 7 of them (including all of the convert group) had better than predicted recovery at 6 months (ARAT 33 - 54, UEFMA 43 - 66), suggesting effectiveness of early and intense hand-focused training. Greater improvement on the ARAT and UEFMA from baseline to 6 months post training in the convert group compared to the negative group [convert group: mean change ARAT=31, UEFMA=34.8, negative group: mean change ARAT=17.1, UEFMA=24.1] likely reflects recovery of corticospinal tract function. Notably, 3 subjects in the negative group also exceeded PREP2 outcomes, perhaps due to the early and intense hand-focused training. Our data suggest that early, intensive hand-focused training featuring virtual reality and robotics may be safe and beneficial to stroke patients with moderate to severe impairment. Additionally, we suggest predictive algorithms should be assessed at later stages of recovery to reflect potential longer-term changes in neural reorganization that may be benefit restitution of function.

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Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: CIHR Grant MOP 106662

ORF Grant ORF-RE 04-47

Title: Persistent motor behaviour impairment after transient ischemic attack

Authors: *L. E. SIMMATIS[1], S. H. SCOTT[1], A. Y. JIN[2]
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Abstract: Background: TIA and minor stroke patients remain at risk of cognitive dysfunction and functional decline despite resolution of acute symptoms. However, the persistence of cognitive, motor, and sensory impairments after TIA is not well-characterized. We performed quantitative robotic assessment of motor behaviour impairment at 4 time points over 1 year in a cohort of TIA/minor stroke patients. **Methods:** Thirty-eight TIA/minor stroke patients were assessed at 2, 6, 12, and 52 weeks after resolution of symptoms using a robotic exoskeleton. TIA/minor stroke patients completed 8 tasks assessing upper limb sensory and motor function, as well as cognitive function. Patient performance was compared to a large database of healthy controls. Impairment was defined as performance below the 5^{th} percentile of healthy controls. Patients were assessed at 2 weeks using the Behavioural Inattention Test (BIT), Montreal Cognitive Assessment (MoCA), and the Chedoke-McMaster Stroke Assessment (CMSA). CMSA was re-assessed at 6, 12, and 52 weeks. MoCA was re-assessed at 52 weeks. Age-related white matter change (ARWMC), the cella-media index (CMI), and diffusion-weighted imaging were assessed in a subset of patients within 2 weeks. **Results:** TIA/minor stroke patients performed significantly below the average for healthy controls on several robotic assessment tasks at all assessment time points. Patient task performances did not significantly differ between 2, 6, 12, and 52 weeks (all $p>0.05$ after Bonferroni correction for multiple comparisons). The average MoCA score within 2 weeks was 26.0±3.5, and 67% of patients had CMSA scores below those of healthy controls within 2 weeks. ARWMC and CMI did not correlate to motor and sensory performance on robotic assessment within 2 weeks; only 1 patient had a restricted diffusion lesion. **Conclusions:** Quantitative robotic assessment showed that TIA/minor stroke patients display a spectrum of cognitive, sensory, and motor impairments that change little over 1 year in spite of initial symptom resolution within 24 hours.

Disclosures: L.E. Simmatis: None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SHS is cofounder and Chief Scientific Officer of BKIN Technologies, the company that commercializes the robotic technology used in this study.. **A.Y. Jin:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.15/X16

Topic: C.08.Stroke

Support: 26350594 (the Japan Society for the Promotion of Science)

17K01482 (the Japan Society for the Promotion of Science)

Title: Effects of various exercises on motor recovery through gating and neuro/gliogenesis in motor cortex infarction in rats

Authors: *T. KUMADA[1], S. MORISHITA[1], K. HOKAMURA[2], A. YOSHIKAWA[3], N. AGATA[1], Y. TSUTSUI[1], K. UMEMURA[2]
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Abstract: Although exercise therapy significantly contributes to the functional motor recovery after cerebral infarction, the neurological mechanisms underlying them remained largely unknown. Since variety types of exercises such as forced treadmill and voluntary exercises can differently affect adult neurogenesis, we have examined the roles of different exercises on neuronal reorganization by newly-generated neural stem cells in motor cortex and motor recovery using a rat model of focal motor cortex infarction. At first, we established rats with focal motor cortex infarction by photochemically induced thrombosis (PIT) method. Focal infarction confined to motor cortex area significantly induced the motor defects by beam-walking analysis, although no significant differences were seen in step length and step width between PIT- and sham-operated rats by footprint analysis. Moreover, three-dimensional gait analysis revealed significant differences in some kinesiological parameters in focal infarcted rats. Next, we examined the effect of the following different exercise programs from 1 day to 4 weeks after surgery: 1) low- and, 2) high-intensity treadmill running, 3) voluntary wheel running, 4) combined exercise programs. Beam-walking tests revealed that motor deficits in exercise groups were significantly reduced compared to those in sedentary groups from 2 weeks after PIT-operation. To evaluate de novo neurogenesis and gliogenesis, we have performed lineage analysis of newly-generating neural (stem) cells using BrdU labeling and immunofluorescence experiments. We will characterize the BrdU-positive cells that enriched in peri-infarct and other areas and discuss the relationship between neurogenesis/gliogenesis and motor recovery.

Disclosures: T. Kumada: None. **S. Morishita:** None. **K. Hokamura:** None. **A. Yoshikawa:** None. **N. Agata:** None. **Y. Tsutsui:** None. **K. Umemura:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.16/X17

Topic: C.08.Stroke

Title: Effects of dominant hand paralysis on performing cognitive tests in stroke patients

Authors: *S. JEE
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Abstract: Introduction: To evaluate the degree to which the paralysis of a dominant hand affects to perform cognitive function in subacute stroke patients

Method: We first recruited 307 patients with subacute hemiplegic stroke to transfer to the rehabilitation department from January, 2015 to February, 2016. At first, we excluded 117 patients of severe cognitive impairment (initial minimal mental status examination < 10). And 11 patients were excluded by age (< 44) and a patient with left dominant hand were also excluded. Finally, 176 patients were dichotomized into two groups according to the sides of lesion (left and right hemisphere). Group 1 consisted of 68 patients whose strokes affected the dominant hand (i.e., right hemiplegia and right dominant hand). Group 2 consisted of 108 patients whose strokes affected the non-dominant hand (i.e., left hemiplegia and right dominant hand). And we devided into the regions of the damaged brain (cortical and subcortical area). The former consisted of 151 patients whose regions of the damaged brain were cortical area and the latter consisted of 25 patients whose regions of the damaged brain were subcortical area. The primary outcome measure was Rey Complex Figure Test, Digit Symbol Coding (DSC) and Trail Making Test (TMT). And we used voxel-based lesion-symptom mapping (VLSM) to analyze the relationship between tissue damage and behavior on a voxel-by-voxel basis, as in functional neuroimaging.
Results: In comparison to Group 1 and Group 2, we did not find any statistically significant differences between the groups in Rey Complex Figure Test, Digit Symbol Coding and Trail Making Test. (Ray raw; p=0.091, Ray Z; p=0.867, DSC raw; p=0.594, DSC Z; p=0.591, TMT A; p=0.721, TMT AZ; p=0.574, TMT B; p=0.061, TMT BZ; p=0.972). However, if the participants were dichotomized by the regions of the damaged brain, we found significant differences between the groups in the cortical regions by Ray raw and TMT B (Ray raw; p=0.037, TMT B; p=0.045).
Conclusion: Although the effect of paralysis on the dominant hand and performing cognitive tests in patients with subacute hemiplegic stroke was not significantly different from the effect of paralysis on the dominant hand, we found that the regions of the damaged brain was significantly different from the effect of paralysis on the dominant hand for performing Ray raw and TMT B. We supposed that this interesting result may be related on the visuo-spatial neglect from cortex lesion.

Disclosures: S. Jee: None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Program#/Poster#: 052.17/X18

Topic: C.08.Stroke

Support: HHS 90IF0090-01-00

NICHD 2RO1HD039343

Title: Evidence for the potential of improving hand function in severely impaired chronic stroke individuals using a device-assisted task specific training: a case series

Authors: C. CARMONA, K. B. WILKINS, J. SULLIVAN, J. DROGOS, J. P. DEWALD, *J. YAO
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Abstract: Purpose: More than two-thirds of people who have had a stroke have difficulty with arm function. Though multiple studies have investigated the effectiveness of several types of interventions, regaining hand function in individuals with severe impairment still remains a challenge. In this study, we explored whether motor recovery or compensation is still possible in individuals with severe chronic stroke when they participate in task-specific practice by using an electrical stimulation device to aid hand opening.
Subjects: Eight participants with chronic stroke (>1-year post, mean: 11.2 years) with moderately to severely impaired upper limb movement (UE Fugl-Meyer (FMA) score 10-24).
Methods: Subjects were recruited to participate in a 20-session intervention (3 sessions/7-8 weeks). During each session, participants performed 20-25 trials of reaching, grasping, retrieving and releasing objects with the assistance of a novel electromyography-triggered functional electrical stimulation system. This system allows for Reliable and Intuitive open of the hand (ReIn-Hand) during multi-joint arm movements. Pre, post, and 3-month follow-up outcome assessments included UE FMA, Chedoke McMaster Stroke Assessment, Grip dynamometry, the Box and Blocks Test, active and passive goniometrics for wrist and metacarpal phalangeal (MCP) flexion and extension (II, V fingers), the Nottingham Stereognosis Assessment (NSA), and the sensory touch threshold using monofilaments.
Results: A non-parametric Friedman test of differences among repeated measures found significant changes in Box and Blocks test scores (x^2=10.38, p< .05), passive and active range of motion (ROM) (x^2=11.3, p< .05; and x^2=12.45, p< .01, respectively), and NSA scores (x^2=6.4, p< .05).
Conclusions: These results suggest that using the ReIn-Hand during reaching and grasping activities may improve sensation and voluntary hand control in individuals with severe impairment following stroke. Specifically, the improved active ROM may suggest an intervention-induced motor recovery.
Clinical Relevance:
Using ReIn-Hand device to facilitate the control of basic hand functions during a task-specific training showed promising results in a small sample size study. Further research is needed to assess the effectiveness of this intervention in randomized control trials with more subjects.

Disclosures: C. Carmona: None. **K.B. Wilkins:** None. **J. Sullivan:** None. **J. Drogos:** None. **J.P. Dewald:** None. **J. Yao:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: NHMRC Grant APP1083209

Title: Hypoxic postconditioning improves functional and histological outcomes following endothelin-1 induced stroke in conscious rats

Authors: *N. M. JONES[1], T. FATH[2], H. L. NGUYEN[3]
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Abstract: Stroke is a common cause of death and a major cause of neurological disability. Current treatment options for acute ischemic stroke are limited to tissue plasminogen activator, but due to its narrow therapeutic window (<4.5h), only 2-5% of patients are eligible for this treatment, highlighting a need to develop novel therapeutic approaches for stroke patients. Recent studies have shown that exposure to intermittent mild hypoxic postconditioning (HPC) can reduce damage after stroke in mice, however, the mechanisms and effects on functional outcomes are not well known. Conscious male Sprague-Dawley rats were subjected to middle cerebral artery (MCA) occlusion by perivascular microinjection of endothelin-1 (ET-1) onto the MCA via a pre-implanted guide cannula. HPC (8% O_2, 1h/d for 5 days) or normoxia (room air, 1h/d for 5 days) treatments were started one day after stroke. Behavioural tests were performed at various time-points (pre- and post-surgery, 1 and 6 days post stroke) to test neurological function. Brains were collected 6 days after stroke and free-floating sections (60μm) were used for histological analysis. The extent of injury was assessed using haematoxylin and eosin and FluoroJade B. Immunohistochemical staining was used to label neurons and astrocytes, using antibodies for neuronal nuclear antigen (NeuN) and glial fibrillary acidic protein (GFAP), respectively. Image analysis was used to quantify changes in brain injury markers. Stroke resulted in functional deficits observed in the tail suspension test, grid-walking task and sensorimotor function. All of these deficits were reduced in stroke animals that received HPC treatment. Following stroke, in the injured (ipsilateral) hemisphere there was an increase in lesion size, FluoroJade B and GFAP staining and NeuN loss in the cortex and striatum. Treatment with HPC after stroke reduced lesion volume and NeuN loss in the cortex, while it increased GFAP staining and the number of FluoroJadeB positive cells in the ipsilateral hemisphere. Our data suggest that HPC-induced neuroprotection was mediated by enhanced astrocyte function, which prevented neuronal loss and reduced infarct volume. All of these processes contributed to enhanced functional recovery after stroke.

Disclosures: **N.M. Jones:** None. **T. Fath:** None. **H.L. Nguyen:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

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Program#/Poster#: 052.19/X20

Topic: C.08.Stroke

Title: Constant cognitive stimulation over a 6-month period improves cognitive function in a vascular dementia-afflicted elder

Authors: *J. G. MARTÍNEZ-GALINDO[1], R. PEDROZA-LLINAS[2]
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Abstract: Numerous reports have found that cognitive stimulation improves the cognitive function in the elderly afflicted with neurocognitive disorders. We present here a case study that supports such finding. We worked with an 81-years-old (at the moment of intervention, July 2015) female patient, diagnosed with vascular dementia (five months prior to intervention), who attended every day an adult-daycare center. Our intervention consisted of 3 non-consecutive sessions a week, for 24 weeks. Each 1-hour session started with a 5 min “warm-up” block (small talk), followed by successive blocks of exercises aimed at working with orientation to reality (time/place/person, 5 min), declarative memory (15 min), attention (15 min), and general cognitive function (such as executive function, reading/writing, visuospatial abilities, etc.; 15 min). Each session ended with a 5-min block to consolidate the work recently done, assess her mood and disposition, etc. Simple tests of memory, language skills, and executive function were done before and after our intervention. We observed an improvement in all cognitive areas explored at the end of the 24 weeks. Our results were accompanied by the subjective report from family members of our patient’s improvement in her general mental state.

Disclosures: **J.G. Martínez-Galindo:** None. **R. Pedroza-Llinas:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: Health Research Council of New Zealand Grant 11/270

Neurological Foundation of New Zealand Project Grant

Title: The PREP algorithm predicts upper limb functional outcomes at 3 months and 2 years post-stroke

Authors: *C. M. STINEAR, M.-C. SMITH, A. BARBER, S. J. ACKERLEY, W. D. BYBLOW
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Abstract: The PREP algorithm can be used within days of stroke to predict upper limb motor outcomes 3 months post-stroke. The algorithm sequentially combines clinical, neurophysiological and neuroimaging measures to predict one of four outcomes for individual patients based on Action Research Arm Test score at 3 months (Excellent, Good, Limited, Poor). The PREP algorithm was recently validated in a study of 192 patients recruited within 3 days post-stroke. The aim of this study is to evaluate whether PREP predictions made at baseline are correct at 2 years post-stroke. Of the 157 patients who completed assessments 3 months post-stroke, 83 patients have completed 2 year follow-up assessments thus far. The PREP prediction at baseline was correct for 70% of patients 2 years post-stroke. Upper limb outcome category was better than predicted for 14% of patients, and worse than predicted for 16%. Upper limb outcome category was stable between 3 months and 2 years post-stroke for 81% of patients. Over this time 11% of patients improved to a better outcome category, and 8% deteriorated to a worse outcome category. There were no differences in baseline age, National Institutes of Health Stroke Scale score, or Charlson Co-morbidity score, between patients whose upper limb outcome remained stable, improved or worsened between 3 months and 2 years post-stroke. Upper limb impairment assessed with the Fugl-Meyer scale was stable between 3 months and 2 years post-stroke for those patients whose functional outcome was stable (mean Δ 1.8 points, 95%CI 0.6 - 3.1). In contrast, Fugl-Meyer scores decreased for patients whose functional outcome worsened (mean Δ -9.6, 95%CI -20.4 - 1.3) and increased for patients whose functional outcome improved (mean Δ 7.2, 95%CI 3.9 - 10.5). Paretic upper limb use was evaluated with the Motor Activity Log (MAL) 6 months and 2 years post-stroke. MAL scores were stable for those patients whose functional outcome did not change (mean Δ 0.1 points, 95%CI -0.2 -0.4) or improved (mean Δ 1.4, 95%CI -0.5 - 3.2). In contrast, MAL scores decreased for patients whose functional outcome worsened (mean Δ -3.8, 95%CI -7.1 - -0.4). These results indicate that PREP algorithm predictions made within days of stroke remain accurate at 2 years post-stroke. They also demonstrate that 3 months is an appropriate time point for upper limb predictions, as impairment, function and use of the paretic upper limb remained stable between 3 months and 2 years post-stroke for the majority of patients. These results confirm that most patients make most of their upper limb recovery during the first 3 months after stroke.

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Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: NIH Grant NS066001

Leducq Foundation Grant 15CVD02

NIH Grant TR001416

Title: Power dynamics underlie pathological spatial synchrony in a rodent model of ischemic stroke

Authors: *R. D. FROSTIG, E. G. WANN
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Abstract: Stroke is the fifth leading cause of death in the United States, and the majority of cases are due to Middle Cerebral Artery (MCA) ischemia (Mozaffarian et al., 2016). Previous studies from our laboratory have demonstrated that sensory stimulation delivered within 2 hours ('early treatment') after permanent MCA occlusion (pMCAo) completely protects the cortex from impending stroke damage, whereas the same intermittent sensory stimulation results in exacerbated damage if delivered 3 hours after ischemic onset ('late treatment') (reviewed in Frostig et al., 2012). The interaction between sensory stimulation treatment and the post ischemic (0-5 hours) neuronal activity could provide a valuable way of assessing how sensory treatment protects the cortex. Using a 32 microelectrode array spanning depths of S1 and neighboring cortical regions, recordings tracked a continuous spatiotemporal profile of local field potentials (LFP) from the MCA territory before (baseline) and directly after (0-5 hours) MCA occlusion in early stimulated, late stimulated, pMCAo alone (control) and sham groups. We found that spatial synchrony, a measure of coordinated neuronal network activity across all recording locations, is increased directly after pMCAo and is persistently high throughout the acute (0-5 hour) post-pMCAo period in animals infarcted 24 hours later (pMCAo alone and late stimulated groups) and, therefore, predicts pathological dysfunction after pMCAo. In early stimulated animals, the absence of high spatial synchrony post-pMCAo is consistent with these animals' protection from stroke. We further revealed that the emergent spatial synchrony post-pMCAo is driven by temporally distinct bursts of power in delta, theta, and alpha bands that also increase in number post pMCAo. This study is supported by NIH Grant NS066001, NIH Grant TR001416, and Leducq Foundation Grant 15CVD02.

Disclosures: R.D. Frostig: None. **E.G. Wann:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: WVCTSI Award U54GM104942

Brain Initiative R24 MH106057-03

Title: Dynamic functional positron emission tomography (fPET) imaging of glucose metabolism during a human ambulation task

Authors: C. BAUER[1], A. STOLIN[2], M. MANDICH[3], B. KUNDU[4], M. MUZI[5], P. E. KINAHAN[6], N. SIVA[2], R. HARRISON[5], J. QI[7], S. DOLINSKY[8], S. MAJEWSKI[4], *J. A. BREFCZYNSKI-LEWIS[2]
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Abstract: Neuroimaging has revealed many intrinsic neural processes in the human brain during a plethora of tasks ranging between sensory, motor, and cognitive functions. However, current techniques have yet to uncover brain neural metabolism during upright human locomotion and balance, despite obvious clinical needs in areas of stroke rehabilitation and other disorders. This study of human ambulation takes advantage of two advances in fPET imaging - a lightweight, wearable PET imager and novel brain imaging techniques that allow sub-minute resolution of task-related glucose metabolism. **Methods:** Using approximately 10% of a standard clinical dose (1-2 milliCuries) of metabolic marker F^{18}-Fluorodeoxyglucose (FDG, 110 minute half-life), we imaged participants who walked vs. stood in place for an alternating on/off block paradigm (30 sec) immediately after dose injection, for a total duration of 6 minutes. In regions of interest (ROI) related to walking in motion (basal ganglia, thalamus, leg/foot primary motor cortex), we compared FDG activity over time during the walking task as well as performed wavelet modeling to pull out independent components associated with task performance. The 6 minute task was followed by a 10 minute time block task of seated walking in place vs. sitting still (5 minutes each). Datasets were corrected for motion, uptake dynamics, and segmenting ROIs based on a normalized FDG atlas. **Results:** Preliminary results indicate that there were significant increases in glucose metabolism during walking compared to rest on a voxel by voxel basis over the first 6 minutes. Metabolism in motor-related regions followed the time curve predicted by task timing following injection. In addition, we replicated the timing parameters from other dynamic PET paradigms showing regional task activity during the 5 minute task vs. 5 minute rest timeperiod. **Conclusions:** We were able to demonstrate early results suggesting that

30-second temporal resolution dynamic PET imaging of human ambulation is feasible. Real time studies requiring locomotion would thus be enabled with a wearable PET scanner that moves with the head, as well as a dynamic PET paradigm with mathematical predictions for the F^{18}-FDG uptake curve. The ability to do this imaging in PET, as opposed to EEG and NIRS, enables imaging of deeper areas of the brain using numerous biological markers. Furthermore, the ability to do this mobile PET imaging with such a low dose of radiotracer enables longitudinal imaging to assess long-term neurological changes. We hope to further extend this application to more natural forward locomotion paradigms, using a frame-supported wearable PET system.

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Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 052.23/X24

Topic: C.08.Stroke

Support: NIH Grant R01 HD084009-01A1

NIH Grant T32EB009406

Title: Voluntary drive of paretic elbow muscles in individuals with chronic hemiparetic stroke: Preliminary findings

Authors: *L. GARMIRIAN, J. DEWALD, A. ACOSTA
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Abstract: Introduction: After a stroke, individuals experience neurological issues due to a unilateral brain injury, which in turn causes deficits including paresis, the inability to efficiently and fully activate muscles. Overtime, paresis, combined with decreased use of the upper extremity, leads to muscle atrophy. It is hypothesized that paresis will cause less torque to be produced per unit volume of muscle and that paresis and decreased use of the paretic limb over time, will cause muscle atrophy.
Methods: Eight subjects post stroke participated in the study. Six subjects completed the muscle volume assessments and two subjects completed the muscle volume assessment and strength testing.
Magnetic resonance images were acquired to determine the volume of contractile tissue in the biceps, brachialis and triceps. A 3D gradient echo pulse sequence was used (TR=7ms, flip

angle=12°, matrix size = 256x216, slice thickness = 3mm). The Dixon method was used to estimate and account for intramuscular fat. Manual segmentations of the muscles of interest were done to determine contractile tissue volume.
To determine elbow flexion and extension strength, subject's forearms were attached to a 6 degree of freedom load cell with the shoulder flexed 15° and abducted 20° and the elbow at 90°. Elbow flexion and extension maximum voluntary torques (MVTs) were measured for the paretic and non-paretic limb.
Results: For all three muscles of interest, the volume of contractile element was significantly smaller ($P<0.05$) in the paretic limb compared to the non-paretic. The paretic flexors were 25% smaller than the non-paretic and the paretic extensors were 30% smaller than the non-paretic. The MVT produced was 50.8 Nm, 38.2 Nm, 22.7 Nm and 13.2NM for the non-paretic elbow flexors, non-paretic elbow extensors, paretic elbow flexors and paretic elbow extensors, respectively.
Subjects were able to generate more torque per unit volume of muscle with their non-paretic limb, compared to their paretic, for both elbow flexors and extensors. Subjects were able to generate 0.16 Nm/cm^3 with their non-paretic elbow flexors and 0.08 Nm/cm^3 with their paretic flexors. Subjects were able to generate 0.11 Nm/cm^3 with their non-paretic elbow extensors and 0.06 Nm/cm^3 with their paretic extensors.
Discussion: Detailed information about the pattern of atrophy and altered voluntary drive will help guide and improve rehabilitation. Future work involves the study of changes in volume and voluntary activation at more distal muscles as well as quantification of voluntary activation through twitch interpolation.

Disclosures: L. Garmirian: None. **J. Dewald:** None. **A. Acosta:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: CIHR Grant MOP 106662

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University of Calgary Eyes High Postdoctoral Fellowship

Title: Size of acute lesion and white matter hyperintensities impact different aspects of sensory, motor, and cognitive recovery post-stroke as measured by robotic tasks

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Abstract: Both acute lesion volume and degree of chronic white matter disease have been deemed prognostic factors in stroke recovery. Clinical metrics used to measure recovery often do not distinguish between specific aspects of sensory, motor, and cognitive recovery. The purpose of this study was to use robotic assessments to determine specific aspects of recovery that are influenced by acute lesion volume and/or chronic white matter disease, as measured by white matter hyperintensities (WMH).
Eighty individuals with first time clinically identified unilateral strokes participated in this study. Acute lesions and WMH were marked on FLAIR images and volumes were measured in standard space. Robotic assessments using the KINARM exoskeleton robot were completed at 1, 6, 12, and 26 weeks post-stroke using standardized tasks: position matching (PM), visually guided reaching (VGR), bilateral object hit (OH), and bilateral object hit and avoid (OHA). Performance on each task was measured by specific parameters and represented by a z-score relative to the performance of a large cohort of control subjects. The number of parameters varied by task, with 4 parameters for PM, 9 for VGR, 14 for OH, and 20 for OHA. An exploratory analysis using linear mixed models investigated the role of lesion volume and WMH volume on performance on each parameter across the four time points.
Lesion volume was a significant explanatory factor for performance across all time points for all parameters of PM- absolute error, variability, contraction/expansion, and shift (β ranged from 0.0098-0.019, where β represents change in z-score for each 1 mL increase in lesion volume). In VGR, lesion volume was a significant explanatory variable only for reaction time (β=0.010). Lesion volume was also an explanatory factor for all OH parameters (β ranged from 0.0077-0.034) except three which describe the movement area of the affected arm and spatial overlap of the two arms. OHA showed similar effects of lesion volume as with OH (β ranged from 0.0057-0.018). WMH only had a significant role in performance on OHA where it was linked to parameters with higher cognitive demands, such as the number of distractors hit, and object processing rate (β ranged from 0.027-0.054).
In summary, acute lesion volume has widespread effects on sensorimotor recovery, while the influence of chronic white matter disease is limited to the more cognitive aspects of sensorimotor tasks. However, based on the coefficients of the linear mixed model, the effects of WMH, when significant, were greater than those of lesion volume. These results demonstrate that while both lesion size and WMH have prognostic roles, they impact different areas of recovery.

Disclosures: R.L. Hawe: None. **S.E. Findlater:** None. **J.M. Kenzie:** None. **M.D. Hill:** None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Scott is cofounder and chief scientific officer of BKIN Technologies, the company that commercializes the KINARM robotic device.. **S.P. Dukelow:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

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NIH R01DC008149

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Title: The impact of stroke on lingual muscle force and fiber type in a rat model

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Abstract: Up to 50% of people have difficulty swallowing (dysphagia) following stroke, which can increase mortality rates, malnutrition, and risk of aspiration pneumonia. Lingual weakness after stroke is associated with dysphagia, and the tongue muscles have been identified as a therapeutic target. The reported effects of stroke on limb muscles include altered myosin heavy chain (MyHC) muscle fiber types as well as reductions in muscle fiber size and number, yet the impact of stroke on the lingual muscles is not known. Understanding changes occurring in the lingual muscles after stroke may help guide clinical research on therapeutic interventions. A widely used animal model of stroke is middle cerebral artery occlusion (MCAO) surgery in the rat, which induces a unilateral transient focal ischemia. We hypothesized that MCAO surgery would result in lingual weakness and shift the MyHC fiber type composition of the contralateral lingual muscles towards faster fiber types, specifically MyHC type IIb. Maximum voluntary tongue pressing forces were determined in 6-week old male Sprague-Dawley rats prior to receiving either a MCAO (N = 6) or sham (N = 5) surgery. Tongue pressing forces were reassessed at one and two weeks post-surgery. MCAO tongue forces were significantly reduced from baseline at 1 and 2 weeks ($p = 0.001$, $p = 0.021$), while sham tongue forces at 1 and 2 weeks were not significantly different from baseline ($p = 0.625$, $p = 0.125$). Additionally, MCAO forces were significantly smaller than sham at both 1- and 2-week time points ($p = 0.011$, $p = 0.024$), but not at baseline ($p = 0.585$). Fluorescent immunohistochemistry was used to assess muscle MyHC fiber types. In the genioglossus, a protrusive lingual muscle, preliminary data indicated a shift in MyHC fiber type composition on the contralateral side, with the percent of fast contracting MyHC IIb fibers increased.

Disclosures: M.J. Cullins: None. **N.P. Connor:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Program#/Poster#: 052.26/X27

Topic: C.08.Stroke

Title: Increased levels of fatigue are associated with deficits in skilled object manipulation following stroke

Authors: K. A. FERCHO, *L. A. BAUGH
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Abstract: For up to 75% of stroke survivors, fatigue in daily life contributes to a lower quality of life, is associated with a higher risk of death, and is ranked by stroke survivors and health professionals as one of the top 10 research priorities relating to life after stroke. With over 610,000 Americans experiencing a first-incident stroke each year, and more than one-third of stroke survivors identifying that fatigue interferes with daily activity, the cause of fatigue following stroke is of paramount importance. To date, models of fatigue in post-stroke patients have been developed that include biological, psychosocial, and behavioral factors. Based on these models, meta-analyses have shown that physical impairments in post-stroke survivors are a significant factor in the development and maintenance of post-stroke fatigue. Currently, there is little understanding as to the causal link between physical impairment and the development of post-stroke fatigue. The presented research examined the relationship between upper-extremity motor deficits in skilled object manipulation and the development of post-stroke fatigue. We predicted that those participants displaying deficits in skilled object manipulation, as assessed through novel object-interaction tasks, would be more likely to report fatigue due to the increased mental workload associated with monitoring and correcting motor errors during task performance. To examine this issue, data was collected from 42 stroke patients displaying upper-extremity deficits as they completed experimental tasks designed to assess distal force production, sensorimotor memory, and sensorimotor integration abilities. Performance on each of these tasks was compared to 50 healthy, age-matched control participants to determine those with performance outside of the normal range. As expected, a significantly increased proportion of those with performance metrics outside of the range of control participants reported fatigue compared to those with performance within the normal range of age-matched control participants. These data provide an initial examination of the link between skilled-motor performance deficits and the development of post-stroke fatigue, and lay the foundation for future work examining the relationship between increases in mental workload due to errors in predictive motor control and development of this debilitating condition.

Disclosures: K.A. Fercho: None. **L.A. Baugh:** None.

Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

Location: Halls A-C

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Topic: C.08.Stroke

Support: OSF ILLINOIS NEUROLOGICAL INSTITUTE

Title: The progression of post-stroke brain damage as function of stages of chronic kidney disease

Authors: *B. CHELLUBOINA[1], K. NALAMOLU[1], J. D. KLOPFENSTEIN[2], D. Z. WANG[3], D. M. PINSON[4], K. VEERAVALLI[1]
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Abstract: The progression of brain damage and recovery after ischemic stroke depends on an array of risk factors. Chronic kidney disease (CKD) is an independent risk factor for ischemic stroke. As it advances, CKD accelerates atherosclerosis, thromboembolism, and hemorrhagic events and modifies the treatment outcome in acute stroke and secondary stroke prevention. However, currently there are very limited evidence-based studies to draw any conclusions for this major clinical problem. The correlation between the stages of CKD and ischemic stroke severity and treatment are not yet established. Based on the reported literature and the results of our preliminary research investigations, we hypothesized that CKD-induced cardio-renal mechanisms exacerbate post-stroke brain damage and limit the functional recovery. To test our hypothesis, we recently developed an adenine diet-induced gradient (1-3weeks) CKD in 4-5 weeks aged male Sprague-Dawley rats. At 9-week age, all the animal groups (No-CKD, 1week-CKD, 2week-CKD and 3week-CKD) were subjected to a two-hour middle cerebral artery occlusion followed by three days' reperfusion. To identify the correlation between the post-stroke severity and stages of CKD, we performed various techniques including TTC staining, Evan's blue extravasation, RT-PCR, immunoblot, immunofluorescence and biochemical analysis. Our results clearly demonstrated a gradient progression of post-stroke severity as the CKD advances. Further, we also identified key molecules, which persistently upregulated after ischemic stroke in normal and CKD animals as well as CKD animals without stroke. Based on our results we conclude that there is a strong correlation between severity of CKD and post-stroke brain damage. Our findings established an appropriate preclinical model to identify novel and potential targets to treat ischemic stroke in CKD subjects, which will eventually establish a new avenue, to develop future stroke therapies to treat stroke in CKD patients.

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Poster

052. Stroke: Automated Assessment, Treatment, and Rehabilitation Tools

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Topic: C.08.Stroke

Support: CNPq Grant 476634/2013-0

Title: Reactive species levels in circulating extracellular vesicles following ischemic stroke - the role on cognitive function

Authors: *I. R. SIQUEIRA, L. CECCHINEL, K. BERTOLDI, E. DA SILVA, A. MAGALHÃES, M. F. CHAVES
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Abstract: The role of reactive species (reactive oxygen species and reactive nitrogen species) in pathogenesis of ischemia-reperfusion has been widely considered. Besides, it has been demonstrated that total reactive oxygen species generation is increased over time in stroke. Although circulating extracellular vesicles can release and/or generate reactive species and exosomes are able to carry antioxidant enzymes, such as superoxide dismutase (SOD), the involvement of oxidative profile of circulating extracellular vesicles in stroke, as well on cognitive function following stroke is still unclear. Our main aim was to investigate the profile of extracellular vesicles in blood of patients treated in a public teaching hospital in Southern Brazil who have confirmed a diagnosis of ischemic stroke without or with cognitive impairment in acute and chronic phases. Mini-Mental State Examination (MMSE) was used as score of cognitive function. The exosomes isolation was performed using a commercial kit (Exiqon, Denmark). The exosomal oxidative state, represented by the reactive species levels and the SOD activity, was altered in the chronic phase when compared to the acute phase. Higher levels of exosomal reactive species in the acute phase were correlated to lower total protein concentrations and AChE activity in the chronic phase of patients with cognitive impairment (lower MMSE scores). In addition, a significant positive correlation between reactive species in the acute phase and SOD activity in the chronic phase was found specifically in patients with cognitive impairment. These associations were not observed in patients without cognitive impairment. Our data indicate that reactive species levels in the acute phase may predict changes in the extracellular vesicles profile in the chronic phase of patients with impaired cognitive function.

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Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 053.01/X30

Topic: C.09. Brain Injury and Trauma

Support: DFG SFB 870

DFG SyNerGy Exc1010

Title: Voluntary exercise accelerates functional recovery and improves spinal cord plasticity following injury in mice

Authors: *K. LOY[1], A. SCHMALZ[1], T. HOCHE[1], A. JACOBI[1], M. KREUTZFELDT[2,3], D. MERKLER[2,3], F. M. BAREYRE[1,4]
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Abstract: Spinal cord injury is a devastating condition with very little treatment options until today. To date, rehabilitation of patients has an increasingly important role to maximize physical capacities and prevent secondary complications and remains the only form of treatment that is beneficial to the patient. The anatomical changes underlying rehabilitation-based functional improvements are however to date still unclear. Therefore in this study, we use a dorsal hemisection model of incomplete SCI in adult mice in combination with voluntary wheel running to mimic voluntary rehabilitation paradigm. We used a combination of behavioral, anatomical, and immunohistological techniques to assess functional recovery and its anatomical correlate following voluntary wheel training and observed that mice with free access to running wheels show a faster and improved recovery of motor function compared to control mice. Our analysis also demonstrated that this faster and better recovery is correlated to improved intrinsic axonal plasticity and a modulation of the environmental barriers in the spinal cord. This study sheds lights on how rehabilitation enhances spinal cord plasticity and is key to the design of new rehabilitation protocols further “train” the spinal cord following injury.

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Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 053.02/X31

Topic: C.09. Brain Injury and Trauma

Title: Lateral olfactory tract usher substance (LOTUS) promoted axonal regeneration and functional recovery after spinal cord injury in adult mice

Authors: *S. ITO[1], N. NAGOSHI[2], O. TSUJI[2], K. KOJIMA[2], S. SHIBATA[2], M. SHINOZAKI[2], M. MATSUMOTO[2], K. TAKEI[3], M. NAKAMURA[2], H. OKANO[2]
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Abstract: [Introduction] Lateral olfactory tract usher substance (LOTUS) can be found as both membrane and secreted protein that functions as a molecule for neuronal circuit formation. LOTUS binds to Nogo receptor 1 and inhibits all of five axonal growth inhibitors, Nogo, MAG, OMgp, BLys, CSPG. It has been reported that, in LOTUS knockout mice, the motor function recovery after SCI is significantly worse when compared with wild-type mice. The purpose of this study is to evaluate the axonal regeneration and motor function recovery after SCI in LOTUS overexpressed mice. [Method] Contusive SCI was induced at the Th10 level in LOTUS-overexpressed mice (LOTUS group; n=20) and wild-type mice (control group; n=16) as reported previously. Hindlimb motor function was evaluated weekly for six weeks using BMS scores; and the DigiGate system and rotarod test was used on the sixth week after SCI. On this sixth week, biotinylated dextran amine (BDA) was injected into the primary motor cortex to trace the corticospinal tract (CST), or fluoro-gold (FG) was injected into the lumbar spinal cord to trace the reticulospinal tract. Two weeks after the injection, electrophysiological analysis using spinal cord-evoked potential was conducted. After the mice were sacrificed, histological analyses were performed. [Result] Significant improvements in BMS scores was seen in the LOTUS group compared with that in the control group at one week following SCI and thereafter (At week six: LOTUS group; 4.13±1.11 vs. control group; 2.25±0.32, $p<0.01$). DigiGate analysis also revealed a significantly longer stride length in the LOTUS group, and the rotarod test showed significant longer total run time in the LOTUS group. Electrophysiological analysis revealed significantly shorter latency and larger amplitude in the LOTUS group. Histological analyses revealed that the NF-H, 5-HT and p-GAP43 positive fibers increased significantly at the caudal sites in the LOTUS group compared to the control group. As for the 5-HT positive serotonergic fibers, a major contributor of motor function, a significant increase was seen in the LOTUS group 14 days after SCI and continued to increase up to 56 days. The CST axons labeled with BDA significantly increased at the rostral sites in the LOTUS group, but not at the caudal sites of the lesion epicenter in both groups. On the other hand, reticular nucleus neurons retrogradely labeled

with FG increased significantly. [Conclusions] LOTUS showed beneficial effects for functional recovery in SCI by promoting axonal regeneration and nerve axonal protection. In the future, we will evaluate the effect of transplantation of LOTUS overexpressed neural stem cells in the injured spinal cord.

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Poster

053. Spinal Cord Injury: Recovery and Repair

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Program#/Poster#: 053.03/X32

Topic: E.09. Spinal Cord Injury and Plasticity

Title: Nucleus accumbens plays an essential role for recovery of finger dexterity after spinal cord injury

Authors: *M. SUZUKI[1,2,4,5,6], K. ONOE[7], M. SAWADA[3,5], N. TAKAHASHI[2,5], N. HIGO[8], Y. MURATA[8], H. TSUKADA[9], T. ISA[2,5], H. ONOE[2,7], Y. NISHIMURA[1,2,5]
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Abstract: Motivation enhances and depression impedes functional recovery after neuronal injury such as spinal cord injury (SCI) and stroke. It is generally thought that the nucleus accumbens (NAc) regulates motivation-driven effort. A recent non-human primate study showed that during early recovery of finger dexterity after SCI the NAc up-regulated the neuronal activity of the primary motor cortex (M1) and was directly involved in the control of finger movements. However, it is still obscure whether the NAc contributes to functional recovery itself. The aim of the present study was to demonstrate the causal role of the NAc in functional recovery of finger dexterity after SCI by observing the recovery course of bilateral NAc-lesioned monkeys.
All 9 monkeys were trained to reach, grasp and retrieve a small piece of food using both the index finger and thumb (precision grip). Monkeys in NAc-lesioned group (n=3) received microinjection of ibotenic acid (15 ug/ul, 1 ul/site, 9 sites/hemisphere) for lesioning the bilateral NAc. Sham lesion group (n=3) received microinjection of saline. NAc lesion itself had no effect on finger dexterity. Then, spinal lesion was made at the border of C4 and C5 segment. Sham

lesion group showed recovery of precision grip after SCI while NAc-lesioned group showed recovery of rough grasping such as power grip but didn't show any recovery of precision grip. To clarify the difference of neural substrate between precision grip and power grip after SCI, we measured regional cerebral blood flow, an index of regional neuronal activity, with positron emission topography before and after SCI while the monkeys (n=3) were performing precision grip or power grip, respectively. Both contralesional-M1 and contralesional-NAc activity increased at recovery stage during precision grip or power grip, respectively. Then, we analyzed functional connectivity between M1 and NAc. M1-NAc connectivity emerged during precision grip only at recovery stage after SCI. However, no significant M1-NAc connectivity was observed during power grip before and after SCI. This result suggested that M1-NAc connectivity was important for recovery of precision grip but not for power grip. This was supposed to be the reason why NAc lesion group didn't show any recovery of precision grip but showed recovery of power grip.
The present study demonstrated that NAc has a causal role in functional recovery of finger dexterity after SCI and that M1-NAc connectivity during recovery process might be necessary to facilitate recovery of finger dexterity.

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Poster

053. Spinal Cord Injury: Recovery and Repair

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Program#/Poster#: 053.04/X33

Topic: C.09. Brain Injury and Trauma

Support: The Swedish Science Research Council

Title: Unilateral brain injury induced spinal plasticity: side-specific opioid mechanism

Authors: *G. Y. BAKALKIN[1], H. WATANABE[1], O. KONONENKO[1], D. SARKISYAN[1], T. IAKOVLEVA[1], N. MARKLUND[2]
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Abstract: OBJECTIVES. the striking phenomenon of spinal cord plasticity induced by brain injury was discovered by Anna Di Giorgio in 1929. In these experiments, unilateral lesion to the cerebellum resulted in hind limbs postural asymmetry exhibited as ipsilateral hind limb flexion. The asymmetry retained after spinal transection suggesting side-specific plastic changes in the spinal cord. We here examined whether focal cortical injury induces similar phenomenon and

searched for underlying neurobiological mechanisms. METHODS. Unilateral cortical injury (ablation by aspiration or controlled cortical impact, CCI both centered on cortical hindlimb representation area) in rats. Behavioral and EMG analysis of postural asymmetry / reflexes. qRT-PCR, ddPCR, IH, ISH. RESULTS. Unilateral cortical injury induced hind limb postural asymmetry that retained after spinal cord transection. The right-side injury resulted in the left hind limb flexion. Administration of the general opioid antagonist naloxone or selective mu-antagonist beta-FNA but not selective delta-antagonist naltrindole inhibited formation of postural asymmetry. Surprisingly, selective kappa-antagonist nor-BNI reversed the side of the flexed leg in CCI rats. The reversion was evident prior to and after spinal transection. Selective kappa-agonists U50488 or dynorphin under i.t. or i.v. administration mimicked the effects of right-side CCI by inducing the left limb flexion in naive animals. Consistently, lateralized expression of opioid receptors was revealed in the spinal cord. CONCLUSIONS. The dynorphin-kappa opioid system is lateralized and as such may be involved in unilateral CCI-induced side-specific plastic changes in the spinal cord. These changes may underlie motor impairment while their targeting by kappa-antagonists may contribute to motor recovery.

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Poster

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Topic: C.09. Brain Injury and Trauma

Title: Lateral olfactory tract usher substance (LOTUS) suppresses astroglial differentiation of neural stem/progenitor cells

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Abstract: [Introduction]
Lateral olfactory tract usher substance (LOTUS) is a guidance substance for the formation of the olfactory bulb in fetal mice. It has an antagonistic effect on Nogo receptor 1 (NgR1) and promotes neurite outgrowth. Meanwhile, a ligand Nogo plays roles not only to inhibit axonal regeneration, but to promote astroglial differentiation of neural stem/progenitor cells (NSPCs). However, it remains elusive about the impact of the LOTUS on glial differentiation or regulation of GFAP promoter. The aim of this study is to evaluate the effects of LOTUS protein administration to NSPCs during differentiation in vitro.

[Methods]
Differentiation assay – NSPCs were prepared from mouse telencephalons at embryonic day (E) 14.5 and cultured with or without recombinant LOTUS protein. 4 and 8 days after LOTUS treatment, immunocytochemical evaluation was performed.
Luciferase assay – NSPCs were transfected with a reporter construct composed of the fire fly luciferase (ffluc) gene and the 2.5 kb mouse GFAP promoter (GF1L-pGL3). Cells were stimulated with LIF or Nogo A for 8 hours with the recombinant LOTUS protein, and luciferase activity was measured. Ffluc activity was compensated by co-transfected sea pansy luciferase activity (pEF-Rluc) as an internal control.
[Results]
In the differentiation assay, the NSPCs successfully differentiated into neurons, astorocytes, and oligodendrocytes in both LOTUS treated and non-treated groups. However, the population of GFAP positive cells decreased significantly in the LOTUS treated group compared with the non-treated group at day 8 (8.6%±2.13% vs. 20.4%±4.1%, $p<0.05$). No significant differences were found between the neuron and oligodendrocyte population. In the luciferase assay, ffluc activity decreased with the stimulation of LIF or Nogo in the LOTUS treated group compared to the non-treated group. These data indicates GFAP promoter activity decreased in the LOTUS group.
[Conclusions]
LOTUS suppresses astroglial differentiation of NSPCs in vitro. In future, we will evaluate its therapeutic effects for spinal cord injury with a combination of NSPC transplantation in vivo study.

Disclosures: **Y. Hoshino:** None. **J. Kohyama:** None. **N. Nagoshi:** None. **O. Tsuji:** None. **S. Ito:** None. **K. Nishide:** None. **M. Matsumoto:** None. **M. Nakamura:** None. **K. Takei:** None. **H. Okano:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 053.06/Y2

Topic: C.09. Brain Injury and Trauma

Support: NIH R01 NS085426 (VJT)

DoD/CDMRP W81XWH-14-1-0605 (VJT)

Craig H. Neilsen Foundation (VJT)

Drexel University Dean’s Fellowship for Excellence in Collaborative or Themed Research (EM)

Title: Pharmacologically inhibiting tumor necrosis factor α signaling diminishes the development of autonomic dysreflexia and ensuing cardiovascular and peripheral immune dysfunction after complete high thoracic spinal cord injury

Authors: *E. MIRONETS[1], V. BRACCHI-RICCARD[4], P. OSEI-OWUSU[2], R. FISCHER[4], J. R. BETHEA[4], T. SALTOS[3], V. J. TOM[3]
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Abstract: Cardiovascular disease and peripheral immune dysfunction are two major causes of mortality and morbidity in people with spinal cord injuries (SCI). This is primarily due to the development of autonomic dysreflexia (AD), a life-threatening syndrome characterized by extreme, sudden bouts of hypertension triggered by sensory stimuli caudal to the injury. AD intensifies partly due to excitability driven by aberrant plasticity of circuits that participate in the spinal sympathetic reflex. Since soluble tumor necrosis factor α (sTNFα) has been correlated with hyperexcitability, we hypothesize its signaling for sustained periods of time plays a crucial role in this plasticity. To test whether sTNFα is key for AD development, after T3 Tx, animals continuously received XPro1595, a biologic that inhibits sTNFα signaling (N=10), or saline (n=9) intrathecally to spinal cord caudal to the SCI for 4 weeks. Using implanted radiotelemeters, at 2, 3 and 4 weeks post-Tx, we assessed both spontaneously occurring AD events over a 24 period and evoked AD using a colorectal distension (CRD). XPro1595 rats had significantly fewer spontaneously occurring events at all 3 testing points than saline animals. XPro1595 rats had significantly smaller and shorter hypertensive episodes during and after CRD. We also assessed peripheral immune function 4 weeks post injury (wpi) by extracting spleens of deeply anesthetized animals and using flow cytometry to assess quantities of immune markers (e.g. B-cells, T-cell, macrophages/monocytes). We found that saline-treated animals showed had significantly fewer B cells and more macrophages/monocytes compared to uninjured animals. However, XPro1595-treated animals had normal numbers of B cells and macrophages/monocytes and significantly more T-regulatory cells, suggesting these animals had more normal immune function. To determine if inhibiting spinal sTNFα signaling affects peripheral vasculature function, we assessed mesenteric arteries from rodents at 4 wpi using ex vivo pressurized vessel recording. Vessels from saline-treated T3Tx rats had increased reactivity to phenylephrine compared to those from both naïve and XPro1595-treated T3Tx rats. Importantly, vessels from XPro1595 rats reacted similarly to naïve vessels. These data suggest that spinal sTNFα signaling after SCI plays a critical role in plasticity leading to AD and ensuing peripheral vasculature and immune dysfunction. This may be attributed to significantly less sprouting of $CGRP^+$ nociceptive afferents in dorsal horn and lamina X and less interneuronal activation upon a below-level sensory stimulus observed in the XPro1595 rats.

Disclosures: E. Mironets: None. **V. Bracchi-Riccard:** None. **P. Osei-Owusu:** None. **R. Fischer:** None. **J.R. Bethea:** None. **T. Saltos:** None. **V.J. Tom:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Topic: C.09. Brain Injury and Trauma

Support: NIH Grant R01 5R01NS082095-03 McTigue (PI)

Title: Green tea extract-rich diet restores hepatic iron regulation but has no effect on hepatic and spinal cord pathology after spinal cord injury in rats

Authors: *M. T. GOODUS[1], A. D. SAUERBECK[1], C. CHITCHUMROONCHOKCHAI[2], R. S. BRUNO[2], P. G. POPOVICH[1], D. M. MCTIGUE[1]
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Abstract: The disruption of autonomic control after spinal cord injury (SCI) impairs the ability of visceral organs to maintain metabolic homeostasis. As a result, individuals with SCI often face chronic medical conditions that negatively impact their health and significantly shorten their lifespan compared to able-bodied individuals. A leading cause of mortality in the SCI population is metabolic dysfunction, and an organ central to metabolic control is the liver. Recent work from our lab showed that inflammatory cytokines, ceramides and lipids accumulate in livers of SCI rats in parallel with morphological signs of macrophage (i.e., Kupffer cell) activation. These changes occur over a period of several weeks after SCI and are symptoms of nonalcoholic fatty liver disease (NAFLD), which is the hepatic manifestation of metabolic syndrome and is associated with insulin resistance, adipose accumulation, and cardiovascular disease - all problems faced by SCI patients to a greater degree than the general population. Green tea extract (GTE) inhibits intestinal lipid absorption and has anti-inflammatory, probiotic, anti-microbial and anti-oxidant properties that ameliorate the effects of NAFLD. Catechins, the major polyphenols in green tea, also mitigate hepatic injury by chelating redox-active metals such as iron, which exacerbates tissue damage and limits functional recovery after SCI. In previous studies, green tea polyphenols were found to be neuroprotective and anti-inflammatory after intraspinal or systemic injections. However, no studies have tested the efficacy of a GTE-rich diet on chronic spinal cord or liver pathology after SCI. Our results verify and extend our prior work by showing increased pro-inflammatory and iron storage genes in the liver 42d post-SCI (dpi). These changes were coincident with increased CD68+ macrophages and lipid, iron and ferritin accumulation in the liver. Serum insulin, glucose and alanine transaminase (ALT) were also significantly increased at 42dpi. Rats that were given a GTE chow containing 30% (w/w) catechins 3 weeks before injury and continuously for 42 dpi had ~50% less hepatic iron accumulation compared to control diet rats. Surprisingly, the GTE-rich diet had no effect on

Kupffer cells, hepatic lipid deposition, serum ALT, insulin and glucose levels. Spinal cord pathology, quantified via spared white matter, macrophage activation and spared neurons also was unchanged by a GTE-rich diet compared to control diet injured rats. Collectively, these results indicate that dietary GTE maintains hepatic iron regulation closer to uninjured levels but has no effects on chronic liver and spinal cord pathology after SCI.

Disclosures: M.T. Goodus: None. **A.D. Sauerbeck:** None. **C. Chitchumroonchokchai:** None. **R.S. Bruno:** None. **P.G. Popovich:** None. **D.M. McTigue:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Topic: C.09. Brain Injury and Trauma

Support: Craig H. Neilsen Foundation Pilot Grant 457508

NIH Grant NS055976

Title: Impact of strength training on neuropathic pain and afferent sprouting after cervical spinal cord injury

Authors: *M. R. DETLOFF[1], A. D. TAMASHIRO-ORREGO[1], A. ONG[1], S. J. CHHAYA[1], L. KRISA[2], J. D. HOULE[1]
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Abstract: More than two-thirds of individuals with spinal cord injury (SCI) develop chronic neuropathic pain. SCI-induced neuropathic pain is associated with both nociceptor hyperexcitability as well as sprouting of primary afferent c fibers that transmit pain information to the spinal cord. Previous research in our lab showed that early, aerobic exercise prevents development of neuropathic pain but does not ameliorate it once established. While locomotor training is used in the clinic, the standard of care in post-SCI rehabilitation focuses on improving muscle strength. This project will determine whether early or delayed strength training after SCI can affect nociceptive afferent plasticity and pain development and persistence after cervical SCI. Female Sprague-Dawley rats (n=46) received a C5 unilateral spinal cord contusion corresponding to handedness. A subset of SCI rats underwent isometric forelimb strength training 5 days/week starting at 5 or 42 days post-injury (dpi) lasting 5 weeks. Briefly, rats complete 50 successful repetitions of at least 50g force in an isometric forelimb pull task to receive a food reward. Mean pulling force returned to near normal after 10 strength training sessions regardless of early or delayed initiation of exercise ($p > .05$ vs baseline). The recovery of

forelimb strength corresponded to improvements in reach-to-grasp behavior as assessed using a single pellet-retrieval task. Delayed strength training reduced paw hypersensitivity and pain behavior as measured by von Frey and mechanical conflict avoidance operant tests compared to unexercised and acute strength training SCI groups ($p<.05$). Three days before sacrifice, rats received microinjection of cholera toxin-B (CTB) into the ulnar nerve to identify large diameter sensory afferents. We are currently completing immunocytochemical and quantitative analysis of SCI lesion severity and the degree of primary afferent sprouting associated with forepaw dermatomes. With the results, we hope to better understand the mechanisms underlying SCI-induced pain, allowing for possible refinement of rehabilitation protocols to reduce chronic pain after SCI.

Disclosures: M.R. Detloff: None. **A.D. Tamashiro-Orrego:** None. **A. Ong:** None. **S.J. Chhaya:** None. **L. Krisa:** None. **J.D. Houle:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Topic: C.09. Brain Injury and Trauma

Support: New World Laboratories

Title: Therapeutic impact of grafted oligogenic-directly reprogrammed neural precursor cells and chondroitinase ABC for chronic spinal cord injury

Authors: *S. NORI[1], J.-E. AHLFORS[2], M. KHAZAEI[1], Y. LIU[1], J. WANG[1], T. FUEHRMANN[3], M. M. PAKULSKA[3], M. HETTIARATCHI[3], P. POON[3], M. S. SHOICHET[3], M. G. FEHLINGS[1,4]
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Abstract: Introduction: Treatment of chronic spinal cord injury (SCI) is challenging due to cellular loss, cystic cavity and the inhibitory influence of the glial scar. Previous research has shown that the combinatorial therapy of neural precursor cells (NPCs) and chondroitinase ABC (ChABC), which degrades chondroitin sulfate proteoglycans (CSPGs), promotes motor functional recovery after chronic SCI. However, the translational potential of NPCs is hindered by limited availability, immunologic complications and ethical concerns. To overcome these challenges, we have developed a novel approach to generate NPCs through direct reprogramming of somatic cells (drNPCs). We differentiate drNPCs into oligogenic cells (drNPC-pro-OPCs) and have demonstrated functional recovery after drNPC-pro-OPCs

transplantation in subacute SCI. To improve cell integration in the chronic phase, a less invasive sustainable delivery system of ChABC via a methylcellulose (MC) hydrogel (MC-ChABC) was used. The purpose of this study is to determine the therapeutic potential of the combinatorial therapy of drNPC-pro-OPCs and MC-ChABC following chronic SCI.
Methods: Adult Rowett Nude rats received clip compression SCI at T7 level. At 6w after SCI, MC-ChABC, MC alone or artificial cerebrospinal fluid (aCSF) were injected intrathecally. At 7w after SCI, drNPC-pro-OPCs or aCSF were injected intraspinally. The following groups were studied: 1) MC-ChABC + drNPC-pro-OPCs (n=12), 2) MC-ChABC + aCSF (n=5), 3) MC + drNPC-pro-OPCs (n=11), 4) MC + aCSF (n=5), 5) aCSF + drNPC-pro-OPCs (n=8), 6) aCSF + aCSF (control group, n=12). During the 19-week post SCI period, functional assessments including BBB, CatWalk system and von Frey test were performed.
Results: Grafted drNPC-pro-OPCs survived within the injured spinal cord and differentiated principally into oligodendrocytes at 19 weeks after SCI without tumor formation. Expression of CSPGs was successfully reduced in MC-ChABC-treated groups. Cell survival rates were higher in the drNPC-pro-OPCs and MC-ChABC combinatorial therapy group than the other groups. Motor function in the combinatorial therapy group was significantly improved as measured by BBB scores and the CatWalk system compared to the control group. Sensory function assessed by von Frey test demonstrated no significant difference among the groups.
Conclusion: The present study demonstrates that the MC-ChABC and drNPC-pro-OPCs mediated strategy induces functionally significant repair and regeneration of the chronic injured spinal cord. These findings may facilitate the clinical application of the combinatorial therapy for patients suffering from chronic SCI.

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Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

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Program#/Poster#: 053.10/Y6

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH U01 EB007615-08

NIH U01 EB015521-05

Title: Online learning of stimuli parameters for standing in spinally stimulated paraplegia

Authors: *Y. SUI[1], J. W. BURDICK[2]
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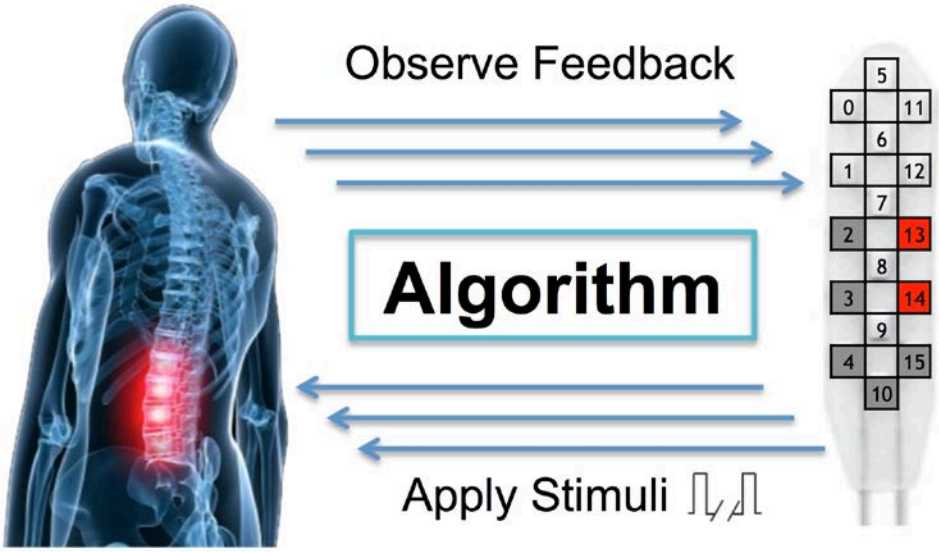
Abstract: Previous research has shown that spinal stimulation via electrode arrays implanted in the epidural space over the lumbosacral area enables paralyzed patients to achieve full weight-bearing standing, improvements in stepping, and partial recovery of lost autonomic functions. The optimal stimulus varies significantly across patients. And even for the same patient, the outcome of the same stimulus varies from trial to trial. Thus, clinicians must determine the optimal stimulus for each patient, under noisy conditions, from a large decision space. Currently, the search for the optimal stimulating parameters is a laborious approach that consumes valuable clinician and patient time, and does not guarantee an optimal outcome.

We developed and tested a *Correlated Dueling Bandit* algorithm to automatically the large decision space of possible stimuli. This algorithms selects and improves the spinal stimulation parameters for standing ability in epidurally stimulated paraplegics, and optimizes them over time. In practice, the algorithm chooses a stimuli, whose effect on the subject is tested and ranked by observing clinicians. The algorithm then balances the exploration for more optimal stimuli while also exploiting currently known good ones to provide effective therapy. The algorithm also seeks to maximize total performance during the limited clinical period within which we can search for the optimal solution.

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. The algorithm chose stimuli that enable the subjects to achieve full weight-bearing standing, consistently improved standing performance over the evaluation period. Moreover, the optimal stimuli sets found by the algorithm included the same stimulating parameters that were selected for each subject by clinical staff using an intuitive search process, validating the effectiveness of the approach.

Figure 1. Closed loop learning of optimal spinal stimuli



Disclosures: **Y. Sui:** None. **J.W. Burdick:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: KAKENHI 15K01378

Title: Recovery of diaphragm motor units activities after cervical hemisection of the spinal cord

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Abstract: A spinal cord injury is accompanied by the varieties of disabilities such as motor and sensory disability. In particular, respiratory disability accompanies high cervical cord injury and there are the clinical cases that patients need the artificial respiration. However, some patients can withdraw from the respirator due to recover their respiratory function. It could be thought that there are varieties of factors which cause the recovery of by the respiratory, and one of the factors could be the plastic change of central nervous system. However, the precise central nervous mechanism is still unknown. The purpose of this study was to examine discharging activities of motor units in the diaphragm on an anesthetized cat of which spinal cord was hemisected three months in advance. Experiments were performed on adult cats. All surgery was done using aseptic techniques. At first surgery animals were anesthetized with Nembutal and we performed the spinal cord hemisected at the junction at the C3/C4 on artificial ventilation. After 3 months spinal cord hemisection animals were reanesthetized with Nembutal and diaphragm motor units were recorded with bipolar needle electrodes under the spontaneous breathing. We monitored ECG, blood pressure, rectal temperature, end-tidal CO_2, and esophageal pressure during the recordings. We judged inspiratory phase from negative phase of esophageal pressure. All the experimental procedures were approved by the Animal Ethics Committee of Ibaraki Prefectural University of Health Sciences.The hemisected side diaphragm motor unit activities were observed in inspiratory phases and ceased in expiratory phases. The recovery of motor unit activities was similar to that of normal diaphragm motor unit activities.This result shows that the phrenic motoneurons can acquire inspiratory synaptic inputs from the respiratory center in the medulla oblongata. The inspiratory neurons in the respiratory center have descending spinal axons and distribute collateral branches in the contralateral phrenic nucleus. These collateral

branches may change after spinal cord hemisection and some collateral branches give synapse to the phrenic motoneurons.

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Poster

053. Spinal Cord Injury: Recovery and Repair

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Program#/Poster#: 053.12/Y8

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH NINDS NS054894

NIH NINDS NS072651

Craig Neilsen Foundation

Title: Investigating functional aspects of optogenetically mediated cortical neuromodulation in T9/T10 complete transected adult rats

Authors: *K. A. SCHMIDT[1], S. F. GISZTER[2]
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Abstract: After a complete T9/T10 spinal cord injury (SCI) in adult rats, trunk control becomes very important for postural stability, and crucial for function if stepping of hindlimbs is enabled. We have developed a neuromodulatory technique aimed at promoting plasticity and motor learning in the trunk motor cortex after SCI via subthreshold optogenetic stimulation using virally delivered Channelrhodopsin (ChR2). Virally delivered enhanced yellow fluorescent protein (EYFP) is used as a control. When light stimulation is paired with a 25 day robot assisted rehabilitation paradigm, motor mapping studies reveal a significant increase in cortical representation of trunk muscle segments below the injury (1-way ANOVA with Tukey-Kramer post-hoc comparisons, $p<0.05$) in the ChR2+robot rats, both with induced spinal stepping (N=8) and without (N=8), but not in EYFP+robot rats with (N=8) or without (N=8) spinal stepping enabled. Further, ChR2+robot rats with stepping show higher percentages of weight supported steps and reduced pelvic roll events compared to EYFP+robot rats with stepping (Wilcoxon rank sum, $p<0.05$). These findings suggest that ChR2+robot rats have learned a greater degree of trunk control above and below the injury, but also, that some of the representation changes resulting from ChR2 occur regardless of stepping ability. Nonetheless, features of pelvic control are enhanced in ChR2 rats that step compared to EYFP rats that also step. How the new cortical controls enabled in ChR2 treated rats are implicated in such functional gains remains unknown.

To probe deeper into these findings, and further understand the interaction between cortex and the injured spinal cord, we propose to conduct chronic trunk electromyogram (EMG) recordings along with intraspinal recordings in four groups similar to those described above throughout the 25 day robot rehab paradigm with light stimulation. EMG recordings will allow us to see the emergence of trunk muscle synergies as rehab progresses, which will inform about functional activity patterns of trunk during walking. As trunk muscle segments below the injury become more active, afferent input to the lumbar spinal cord will be altered. Intraspinal recordings will be able to capture these changes, and provide information about the plasticity of the spinal cord activity after injury in the different cortex treatments. Information gathered in this study will shed light on the mechanisms supporting functional gains achieved after increasing and training cortical trunk control after SCI. This work is supported by NIH NINDS NS054894, and NS072651 and the Craig Neilsen Foundation.

Disclosures: K.A. Schmidt: None. **S.F. Giszter:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: Japan Society for the Promotion of Science, Tokyo, Japan

Title: The anatomical plasticity after spinal lesion in common marmosets

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Abstract: Voluntary movement is strictly impaired by the lesion of cortiospinal connections. We investigated the anatomical changes in corticospinal tract (CST) with hemispinalized common marmosets. The common marmoset is (*callithrix jacchus*) has been attracting much attentions in the field of neuroscience because of its relative ease in handling owing to its small size, and advantages in its unique behavioral and cognitive characteristics (Okano *et al*, Nature, 2009). The anatomy of the marmoset cerebrum has been reported to be similar to those of macaque monkeys and humans; for example, although compact brain size and no central sulcus, they have well developed frontal cortex and clear separation of the primary motor cortex to the somatosensory cortex (Burish *et al*, J Comp. Neuro., 2008). A test was conducted to evaluate motor function disorder, all of the parameters of motor performance examined in the present study showed a significant decrease immediately after injury, with gradual recovery to 55.5 % for 12 weeks after SCI. Especially rising of the shoulder was not improved even after a long

period of injury. In order to quantitatively evaluate the axons in the spinal segment in where neurons which innervate to the hand and arm muscles are exist, the biotinylated dextran amine (BDA) was injected into the forelimb area of the primary motor cortex (M1) to anterogradely label CST axons. We already reported the CST profiles of healthy marmoset (Yoshihara *et al*., NeuroSci. Res., 2015), CST axons mainly descend contra-lateral to the BDA injected side of M1. From that results, we injected BDA into the M1 at the contra-lateral side to the lesion, herewith, we were able to evaluate the compensate projections from intact side of spinal cord to the lesion side. BDA labeled axons were counted in the dorsolateral, ventromedial and dorsal funiculi on both side to the BDA-injection. Terminal buttons were calculated in the Rexed's lamina I ~ XI at the caudal segment to the lesion. Descending axonal density was 1.25 folds increase in contra-lateral to the lesion funiculus compared with in that of intact monkeys, but the population of ipsi-lateral funiculus were disappeared. Many re-crossing axons were observed at below the lesion level, terminal buttons of those axons were 4.4 ± 2.3 % in VII and 2.9 ± 1.1 % in lamina VIII at ipsi-lateral hemicord, but there was no significant differences comparing intact groups (P=0.9 and 0.8, respectively). In consideration of these moderate anatomical changes and incomplete motor recovery, some therapeutics are necessary to re-build neural pathways.

Disclosures: **K.S. Yoshino:** None. **T. Kondo:** None. **M. Nakamura:** None. **H. Okano:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Program#/Poster#: 053.14/Y10

Topic: E.09. Spinal Cord Injury and Plasticity

Title: Promotion of nerve regeneration and functional recovery after spinal cord injury by an endogenous Nogo receptor antagonist LOTUS

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Abstract: After spinal cord injury (SCI), primates, such as humans, hardly recover the locomotor function, but rodents, such as mice and rats, show a partial spontaneous recovery of the locomotor function. However, the factors associated with this partial improvement of nerve regeneration after SCI in rodents remain completely unknown. It has been considered that limitation of neuronal regeneration is mainly caused by axon growth inhibitors such as Nogo proteins, myelin-associated glycoprotein, oligodendrocyte myelin glycoprotein, chondroitin sulfate proteoglycans and B lymphocyte stimulator and a common receptor of these ligands, Nogo receptor-1 (NgR1). We previously identified lateral olfactory tract usher substance (LOTUS) serving as an endogenous NgR1 antagonist. LOTUS suppressed axonal growth inhibition induced by interaction between these NgR1 ligands and NgR1. Therefore, LOTUS

may be useful in future therapeutic approaches as an endogenous potent inhibitor of NgR1 for promoting neuronal regeneration. First, we found that *lotus*-deficient mice showed delayed locomotor functional recovery after SCI, suggesting that LOTUS may be involved in spontaneous recovery after SCI. Next, we also found that LOTUS expression is down-regulated in injured site of wild type mice. The down-regulation of LOTUS expression well associated with decrease of locomotor activity after SCI. Then, we hypothesized that supply of LOTUS could promote spontaneous recovery. To examine effects of overexpression of LOTUS on the recovery of the locomotor function after SCI, we generated the SCI animal model using *lotus*-transgenic (LOTUS-Tg) mice showing overexpression of LOTUS. We clearly found functional recovery of behavioral outcome in BMS locomotor score, footprint and grid walking test in LOTUS-Tg mice. Furthermore, we detected that increase of serotonin-positive regenerating axon and expression of GAP-43, growth associated protein marker in the spinal cord of LOTUS-Tg mice after SCI. These findings suggest that LOTUS may contribute to promotion of nerve regeneration and functional recovery after SCI.

Disclosures: **T. Hirokawa:** None. **Y. Kurihara:** None. **K. Takei:** None.

Poster

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: GACR 17-11140S

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"Centre of Reconstructive Neuroscience " NO: CZ.02.1.01/0.0./0.0/15_003/0000419

project “BIOCEV” (CZ.1.05/1.1.00/02.0109)

Title: The use of hydrogel seeded with iPS-derived neural progenitors in the treatment of chronic spinal cord injury

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Abstract: Spinal cord injury (SCI), is a devastating condition leading to loss of locomotor and sensory function below the injured segment. Despite some progress in acute SCI treatment using stem cells and biomaterials, chronic SCI remains to be addressed. We have assessed the use of laminin coated hydrogel based on poly (2-hydroxyethyl methacrylate), PHEMA with dual porosity, seeded with induced pluripotent stem cell derived neural progenitors (iPSC-NPs), in the treatment of chronic SCI. IPSC-NPs cultured for 3 weeks in hydrogel in vitro were positive for nestin, GFAP and MAP2. These cell-polymer constructs were implanted into rats with balloon compression lesion 5 weeks after lesion induction. Animals were behaviorally tested, and spinal cord tissue was immunohistochemically analyzed 4 months later. The implanted iPSC-NPs survived in the scaffold for the entire experimental period. Host axons, astrocytes and blood vessels grew into the implant and an increased sprouting of host TH^+ fibers was observed in the lesion vicinity. Despite cavity bridging and robust survival of iPSC-NPs in the hydrogel, no statistically significant improvement of locomotor recovery was observed. The implantation of iPSC-NP- cell polymer construct into the chronic SCI led to the integration of material into the injured spinal cord, reduced cavitation and modest behavioral recovery support with no negative impact on treated animals. However, further co-therapies that will augment the efficacy of neural cell transplant and restore function in chronic SCI, have to be identified.

Disclosures: P. Jendelova: None. **J. Ruzicka:** None. **N. Romanyuk:** None. **K. Jirakova:** None. **A. Hejcl:** None. **O. Janouskova:** None. **M. Bochin:** None. **M. Pradny:** None. **L. Vargova:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

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Program#/Poster#: 053.16/Y12

Topic: C.09. Brain Injury and Trauma

Support: Indiana Spinal Cord and Brain Injury Research Fund (INSCBIRF)

Indiana University FRSP-ER

Title: Protective effects of estradiol and dihydrotestosterone following spinal cord injury

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Abstract: Spinal cord injury (SCI) results in large necrotizing lesions that destroy tissue and disrupt spinal tracts, leading to deficits in locomotor and autonomic function. We have

previously demonstrated that surviving motoneurons, and the muscles they innervate, show pronounced atrophy after SCI. We have further demonstrated that SCI-induced motoneuron and muscle atrophy are prevented by treatment with testosterone. In this experiment, we assessed if the active metabolites of testosterone, estradiol (E) and dihydrotestosterone (DHT) have similar protective/therapeutic effects after SCI. Young adult female rats received a T9 spinal cord contusion injury (10 g, 25 mm) using an NYU impactor. Immediately following contusion, rats were implanted with subcutaneous Silastic capsules filled with E, DHT, both hormones, or left blank. An additional group of age-matched, sham-lesioned females served as normal controls. Locomotor testing (BBB) was performed weekly, and voiding behavior was assessed at 3 weeks post-injury. Four weeks after SCI, motoneurons innervating the vastus lateralis muscle of the quadriceps were labeled with cholera toxin-conjugated HRP, and dendritic arbors were reconstructed in 3 dimensions; lesion volume, and tissue sparing were also assessed, as were muscle fiber cross-sectional area. Locomotor behavior improved after SCI, plateauing at 3 weeks (average BBB score = 15.1), but hormone treatment had no effect. Void frequency decreased and void volume increased after SCI; both significantly improved by treatment with either E or DHT, and combined treatment was maximally effective. Contusion injury resulted in large spinal cord lesions; treatment with E attenuated lesion volume, but treatment with DHT or E+DHT were ineffective. Similar effects were present in percent total volumes of lesion, and spared white or gray matter. SCI resulted in a significant decrease (almost 50%) in motoneuron dendritic length; dendritic atrophy was attenuated by treatment with E, DHT, or both combined. Similarly, the vastus lateralis muscle fiber cross-sectional areas of untreated SCI animals were significantly smaller (reduced 25%) than those of sham-surgery controls; muscle fiber areas were not affected in E-treated SCI animals, but were increased after treatment with either DHT or E+DHT. These findings suggest that the deficits in micturition and regressive changes in motoneuron and muscle morphology seen after spinal cord injury can be ameliorated by treatment with E or DHT, further supporting a role for steroid hormones as neurotherapeutic agents in the injured nervous system.

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Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 053.17/Y13

Topic: C.09. Brain Injury and Trauma

Support: International Foundation for Research in Paraplegia (IRP)

Michel-Adrien Voirol Foundation

Firmenich Foundation

Pictet Group Charitable Foundation

Panacée Foundation

Canton du Valais

Wings for Life

Title: Spatiotemporal neuromodulation of the spinal cord combined with robot-assisted training in humans with spinal cord injury (STIMO): Technological and conceptual framework

Authors: *C. G. LE GOFF[1,3], F. B. WAGNER[1], J.-B. MIGNARDOT[1,3], M. CAPOGROSSO[6], I. SEÁÑEZ-GONZÁLEZ[1], M. CABAN[7], R. HEIMGARTNER[1], N. FUMEAUX[1], F. RASCHELLA[2], A. WATRIN[7], M. VAT[4,7], M. AVANTHAY[3], I. FODOR[3], K. VAN DEN KEYBUS[3], G. EBERLE[3], B. SCHURCH[3,5], S. CARDA[3], E. PRALONG[4], M. BOLLIGER[8], J. VON ZITZEWITZ[1], R. BUSCHMAN[9], N. BUSE[9], V. DELATTRE[7], S. MICERA[2,10], T. DENISON[9], H. LAMBERT[7], A. CURT[8], K. MINASSIAN[1,11], J. BLOCH[4,3], G. COURTINE[1,3]
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Abstract: We previously showed that spatiotemporal neuromodulation of the lumbar spinal cord enables the control of flexion and extension of paralyzed legs in animal models of spinal cord injury. Gravity-assisted gait rehabilitation enabled by this neuromodulation promoted a neuroplasticity of residual descending pathways that restored supraspinal control of leg motor control after spinal cord injury. Here, we introduce the technological and conceptual framework of the clinical study STIMO. The objective of STIMO is to evaluate the immediate effects of spatiotemporal neuromodulation on leg motor control, and the long-term effects of an extensive gravity-assisted training on motor recovery in eight participants with a chronic, incomplete spinal cord injury. STIMO exploits an implantable pulse generator with real-time triggering capabilities that allows closed-loop control of epidural electrical stimulation of the lumbar spinal cord. We designed and implemented wireless control systems that linked detection of residual leg movements to adjustment of the spatial location, temporal structure and parameters of stimulation. During training, a robotic platform assists trunk movements in order to maximize gravity-dependent gait interactions during highly participative locomotion within a large and safe environment. An algorithm automatically configures multidirectional forces applied to the trunk based on patient-specific needs. This gravity-assist enables natural walking in non-ambulatory individuals. In addition, monthly evaluations are performed to assess the neuromuscular and biomechanical evolution of the trained individuals. This unified framework provides a cutting-edge environment to evaluate and train individuals with spinal cord injury and offers the tools to

gain insights into the potential of this combined treatment to augment neural plasticity and functional recovery after spinal cord injury.

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Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 053.18/Y14

Topic: C.09. Brain Injury and Trauma

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FNS grant NeuGrasp [205321_170032]

ERC

Wyss Center for Bio and Neuroengineering

Bertarelli Foundation

Title: Hybrid peripheral-spinal neuromodulation therapies enable refined locomotion after paralysis by combining global and local control of leg movements

Authors: *S. M. WURTH[1,2], J. GANDAR[2], M. CAPOGROSSO[2,3], A. CUTRONE[4], S. RASPOPOVIC[1,4], N. PAVLOVA[2,5], P. SHKORBATOVA[2,5], L. BAUD[2], E. D'ANNA[1], Q. BARRAUD[2], K. MINASSIAN[2], F. WAGNER[2], S. MICERA[1,4], G. COURTINE[2]
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Abstract: Electrical spatiotemporal neuromodulation of the lumbar spinal cord enabled controlling extension and flexion of paralyzed legs after spinal cord injury, both in animal models and humans. However, this stimulation protocol is not selective enough to modulate the distal musculature independently and efficiently, impeding a refined movement execution. Peripheral nerve stimulation selectively activates passing axons, which allowed precise control over agonist and antagonist muscles of the ankle in animal models. These results suggest that combined electrical stimulation of both spinal cord and peripheral nerves may provide a global and local control over leg movements, respectively. To evaluate this complementarity, we developed a hybrid neuroprosthetic system that targeted the spinal cord with epidural electrical stimulation and both sciatic nerves with intraneural electrodes in rat models of leg paralysis. Real-time control of peripheral nerve stimulation allowed the selective and graded tuning of distal leg movements, which was not possible with electrical spinal cord stimulation. This local stimulation enabled paralyzed rats to walk over ground and to climb a staircase. Preliminary results in humans suggested similar synergies between spatiotemporal neuromodulation of the lumbar spinal cord and peripheral nerve stimulation. These findings open promising perspectives for the development of hybrid neuroprosthetic systems to restore functional leg movements after spinal cord injury, and potentially other neurological disorders.

Disclosures: S.M. Wurth: None. **J. Gandar:** None. **M. Capogrosso:** None. **A. Cutrone:** None. **S. Raspopovic:** None. **N. Pavlova:** None. **P. Shkorbatova:** None. **L. Baud:** None. **E. D'Anna:** None. **Q. Barraud:** None. **K. Minassian:** None. **F. Wagner:** None. **S. Micera:** None. **G. Courtine:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: C.09. Brain Injury and Trauma

Support: International Foundation for Research in Paraplegia (IRP)

Michel-Adrien Voirol Foundation

Firmenich Foundation

Pictet Group Charitable Foundation

Panacée Foundation

Canton du Valais

Wings for Life

Title: Spatiotemporal neuromodulation of the spinal cord combined with robot-assisted training in humans with spinal cord injury (STIMO): Immediate effects

Authors: *F. B. WAGNER[1], J.-B. MIGNARDOT[1,3], C. G. LE GOFF[1,3], M. CAPOGROSSO[6], I. SEÁÑEZ-GONZÁLEZ[1], M. CABAN[7], R. HEIMGARTNER[1], N. FUMEAUX[1], F. RASCHELLA[2], A. WATRIN[7], M. VAT[4,7], M. AVANTHAY[3], I. FODOR[3], K. VAN DEN KEYBUS[3], G. EBERLE[3], B. SCHURCH[3,5], S. CARDA[3], E. PRALONG[4], M. BOLLIGER[8], J. VON ZITZEWITZ[7], R. BUSCHMAN[9], N. BUSE[9], V. DELATTRE[7], S. MICERA[2,10], T. DENISON[9], H. LAMBERT[7], A. CURT[8], K. MINASSIAN[1,11], J. BLOCH[4,3], G. COURTINE[1,3]
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Abstract: We report the immediate effects of spatiotemporal neuromodulation of the lumbar spinal cord on leg motor control in individuals with incomplete spinal cord injury. This spatiotemporal neuromodulation aims at activating or reinforcing the activity of muscle groups underlying the extension and flexion of distal and proximal limbs during locomotion. Individuals with incomplete spinal cord injury were enrolled in the STIMO clinical study. After surgical implantation of an epidural electrode array, we personalized the spatial location, temporal structure and stimulation parameters of the neuromodulation strategy. First, we assessed the ability of each electrode configuration to access specific groups of leg muscles using electrophysiological recordings of the motor responses, i.e: the spatial location of stimulation,and verified the ability of these electrode configurations to elicit selective flexion and extension contractions of each joint of the legs. Then, we identified the optimal temporal structure to activate these electrode configurations in order to optimally recruit motoneurons activation. Application of these spatiotemporal neuromodulation strategies during overground locomotion with robotic assistance resulted in considerable immediate facilitation of leg kinematics and muscle activity. These spatiotemporal neuromodulation strategies enabled robust motor activity throughout gait rehabilitation. Moreover, these preliminary results provide important insights for the development of neuroprosthetic systems that facilitate walking in paraplegic individuals.

Disclosures: J. Mignardot: None. **C.G. Le Goff:** None. **M. Capogrosso:** None. **I. Seáñez-González:** None. **M. Caban:** A. Employment/Salary (full or part-time):; G-Therapeutics. **R. Heimgartner:** None. **N. Fumeaux:** None. **F. Raschella:** None. **A. Watrin:** A. Employment/Salary (full or part-time):; G-Therapeutics. **M. Vat:** A. Employment/Salary (full or part-time):; G-Therapeutics. **M. Avanthay:** None. **I. Fodor:** None. **K. Van Den Keybus:**

None. **G. Eberle:** None. **B. Schurch:** None. **S. Carda:** None. **E. Pralong:** None. **M. Bolliger:** None. **J. von Zitzewitz:** A. Employment/Salary (full or part-time):; G-Therapeutics. **R. Buschman:** A. Employment/Salary (full or part-time):; G-Therapeutics. **N. Buse:** A. Employment/Salary (full or part-time):; Medtronic. **V. Delattre:** A. Employment/Salary (full or part-time):; G-Therapeutics. **S. Micera:** None. **T. Denison:** A. Employment/Salary (full or part-time):; Medtronic. **H. Lambert:** A. Employment/Salary (full or part-time):; G-Therapeutics. **A. Curt:** None. **K. Minassian:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); G-Therapeutics. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); G-Therapeutics.

Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 053.20/Y16

Topic: C.09. Brain Injury and Trauma

Support: NCCR : SNSF NCCR Robotics Regait 51NF40_160592

SpineRepair : SNSF Nano-tera.ch 20NA21_145923

Title: A transversal epidural electrode array for selective multipolar stimulation of spinal cord sensorimotor circuits

Authors: *J. GANDAR[1], M. CAPOGROSSO[2], N. WENGER[3], F. MICHOUD[4], N. GREINER[5], A. MORTERA[6], P. SHKORBATOVA[6], S. MICERA[9], S. P. LACOUR[7], G. COURTINE[8]
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Abstract: Epidural electrical stimulation (EES) of lumbosacral segments improve motor control after spinal cord injury in animal models and human patients. A growing body of evidences from computational and experimental studies suggests that EES recruits large myelinated afferents in the dorsal roots and increases the excitability of spinal sensori-motor circuits. However, the design of clinical epidural arrays does not reflect the somato-topography of the dorsal roots severely thus affecting the specificity that could be achieved in human patients. Here, we integrated detailed anatomical data of the rat spinal cord with computer simulations to design a novel spinal implant targeting dorsal roots at the sacral spinal cord. Using optimization algorithms we then identified multipolar configurations targeting modulated single dorsal roots,

and thus eliciting specific movements of extension and flexion of the legs. We then fabricated soft neural implant based on this concept and validated model-driven stimulation protocols in rats with chronic spinal cord injury. Our novel interface achieved superior specificity compared to classical interfaces. Moreover, compared to continuous stimulation paradigms, closed-loop control of multipolar stimulations significantly ameliorated gait execution. These findings open perspectives for the development of selective interfaces to specifically target dorsal roots and improve motor control in people with spinal cord injury.

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Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

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Program#/Poster#: 053.21/Y17

Topic: C.09. Brain Injury and Trauma

Support: ERC 588133

SNF Sinergia 513843

Title: Cortico-reticulo-spinal circuit reorganization reverses paralysis after severe spinal cord contusion

Authors: C. KATHE[1], L. ASBOTH[1], L. FRIEDLI[1], J. BEAUPARLANT[1], C. MARTINEZ-GONZALEZ[1], S. ANIL[1], E. REY[1], L. BAUD[1], G. PIDPRUZHNYKOVA[1], M. A. ANDERSON[1], P. SHKORBATOVA[1], J. KREIDER[1], B. SCHNEIDER[2], *Q. BARRAUD[1], G. COURTINE[1]
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Abstract: Severe spinal cord contusions interrupt nearly all brain projections to lumbar circuits producing leg movement. Failure of these projections to reorganize leads to permanent paralysis. Here, we modeled these injuries in rodents. We found that a severe contusion abolishes all motor cortex projections below injury. Using mice expressing light-sensitive channels in cortical projection neurons, we found that electrochemical neuromodulation of the lumbar spinal cord enabled the hindlimb motor cortex to regain a graded control over hindlimb locomotor movements in otherwise paralyzed animals. Virus-mediated tract tracing and circuit-specific inactivation techniques revealed that the cortical drive accessed the lumbar spinal cord through glutamatergic reticular neurons with residual projections below the injury. Gravity-assisted

rehabilitation enabled by electrochemical neuromodulation reinforced these reticulospinal projections, rerouting cortical information through this pathway. This cortico-reticulo-spinal circuit reorganization mediated a motor cortex–dependent recovery of walking and swimming without requiring neuromodulation. Similar mechanisms may improve functional recovery in humans.

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Poster

053. Spinal Cord Injury: Recovery and Repair

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Topic: C.09. Brain Injury and Trauma

Support: International Foundation for Research in Paraplegia Chair in Spinal Cord Repair

Bertarelli Foundation Chair in Translational Neuroengineering

Title: Dimensions matter: Why do the spinal cords of humans and rodents respond differently to epidural electrical stimulation

Authors: *E. FORMENTO[1], M. CAPOGROSSO[2], K. MINASSIAN[1], F. B. WAGNER[1], J.-B. MIGNARDOT[1], C. G. M. LE GOFF[1], T. MILEKOVIC[3], E. BEZARD[4,5,6], J. BLOCH[7], S. MICERA[1], G. COURTINE[1]
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Abstract: Electrical neuromodulation of the spinal cord reversed leg paralysis in rodent and primate models of spinal cord injury (SCI), but has not mediated similar effects in people with paraplegia. Here, we combined computational modelling and experimental procedures in rodents, nonhuman primates and humans to decipher species-specific effects of epidural electrical stimulation (EES) on the production of leg movements. Computer simulations showed that EES interacts with proprioceptive feedback circuits that are naturally modulated during movement and critically contribute to motor pattern formation, both in rodents and humans.

However, anatomical differences between rodents and humans dramatically alter these interactions. We found that the probability of antidromic collisions between EES-induced activity and movement-related information augments with the increase in afferent fibers length. Consequently, continuous EES disrupted the modulation of proprioceptive feedback circuits in humans, which strongly diminished the facilitation of movements with EES. We validated these results in rodents and humans with incomplete SCI. While continuous EES enabled robust locomotion in rats, the limited range of functional EES parameters prevented a similar facilitation of gait in humans. Simulations identified two stimulation strategies that effectively limited the cancellation of proprioceptive information. These strategies involved high-frequency low amplitude stimulation, and EES protocols encoding the natural proprioceptive information in the temporal and spatial structure of stimulation. We validated both strategies in nonhuman primates, whose anatomical properties are comparable to humans. While continuous EES induced co-activation of leg muscles, spatiotemporal EES enabled alternating extension and flexion movements of a paralyzed leg. These findings establish a mechanistic framework to design neuromodulation therapies that enable motor control in humans.

Disclosures: **E. Formento:** None. **M. Capogrosso:** None. **K. Minassian:** None. **F.B. Wagner:** None. **J. Mignardot:** None. **C.G.M. Le Goff:** None. **T. Milekovic:** None. **E. Bezard:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); founder and shareholder of G-Therapeutics SA. **S. Micera:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); founder and shareholder of G-Therapeutics SA. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); founder and shareholder of G-Therapeutics SA.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Program#/Poster#: 053.23/Z1

Topic: C.09. Brain Injury and Trauma

Support: R01HD080205

1R01EB007615-01A1

OICB140483

Title: Spinal cord epidural stimulation effects on urogenital and bowel outcomes

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Abstract: Spinal cord injury (SCI) results in profound changes to sensorimotor as well as autonomic systems. Deficits in urogenital and bowel function after spinal cord injury profoundly impact quality of life and are ranked as top priority issues in the SCI population. Bladder dysfunction may manifest as a failure to store, characterized by uninhibited bladder contractions and an areflexic outlet or as a failure to empty with an areflexic bladder and a sphincter that is unable to relax. Urinary retention and an inability of the bladder to store urine under appropriately low pressures can lead to infection and ultimately impact renal health. Bowel issues such as frequent constipation can trigger blood pressure increases associated with autonomic dysreflexia. The impact of injury on sexual function includes impairments in genital responses in both male and females. While standard pharmacological therapy aims to manage the prevalent urogenital and bowel issues, therapies addressing recovery of function are still needed. Thus, the objective of this study is to describe the effects of spinal cord epidural stimulation as an alternative approach to improve bladder, bowel and sexual function after SCI. This study included AIS grade A and B subjects (n=8) receiving spinal cord epidural stimulation at L1-S1 spinal levels in combination with activity-based therapy: locomotor and/or stand training, cardiovascular and voluntary motor training by our research team. Urodynamic assessments, with and without the use of spinal cord epidural stimulation, at pre- and post-training time-points and the Spinal Cord Injury Data Set questionnaires for bladder, bowel and sexual function management accompanied each urodynamic procedure. We identified specific configurations and stimulation parameters optimal for continence and micturition in several subjects during filling cystometry. While activity-based therapies have resulted in improvements in bladder capacity and voiding efficiency, this study provides evidence that the use of spinal cord epidural stimulation can further enhance these parameters and in a frequency-dependent manner. Importantly, as capacity increased in these participants, bladder pressures continued to remain low, indicating better compliance. Several participants reported reductions in the time required for defecation post-training as well as enhanced ejaculatory ability. Spinal cord epidural stimulation, along with activity-based training, may help provide an appropriate level of excitation to the spinal cord, targeting the neural circuitry involved in urogenital and bowel function.

Disclosures: A.N. Herrity: None. **C.A. Angeli:** None. **E. Rejc:** None. **S.J. Harkema:** None. **C.H. Hubscher:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 053.24/Z2

Topic: C.09. Brain Injury and Trauma

Support: Craig H. Neilsen Foundation

Leona M. and Harry B. Helmsley Charitable Trust

Christopher and Dana Reeve Foundation

Title: Improved respiratory motor control and pulmonary function outcomes after epidural stimulation

Authors: *B. DITTERLINE[1,2], S. C. ASLAN[1,2], C. A. ANGELI[3,1], S. J. HARKEMA[1,2], A. V. OVECHKIN[1,2]
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Abstract: Persons with spinal cord injury (SCI) demonstrate impairment to respiration and pulmonary function outcomes, particularly outcomes that require recruitment of abdominal muscles. This impairs cough and airway pressure generation, which can lead to mucus retention, atelectasis, and ultimately increase the risk of developing pulmonary diseases. In fact, pulmonary disease is one of the leading causes of death in SCI (NSCISC 2015). This makes treatment and prevention paramount in this population.
We found previous success utilizing epidural stimulation of the spinal cord (scES) in facilitating voluntary motor activity of the trunk and lower limbs, which led us to investigate the effects of scES on respiratory motor control. Three individuals participated in this study: A41, a 26 year old male with a C6, AIS-B, SCI; B21, a 32 year-old male with a C4 AIS-B SCI; and A68, a 35 year-old male with a C5, AIS-A SCI. Each individual was implanted with a Medtronic 5-6-5 electrical epidural stimulator on the lumbar spinal cord. After implantation, baseline measurements of maximum expiratory airway pressure generation (PE_{max}, cmH_2O) and standard spirometric outcomes (Forced Vital Capacity [FVC] and Forced Expiratory Volume in 1s [FEV_1]) concurrent with surface electromyography (sEMG) of upper trapezius, intercostal, rectus abdominus, and oblique muscles were obtained. Individuals then participated in 80 sessions of scES training, in which the stimulator was turned “on” for 120 minutes, 5 days a week. This was followed by an additional 80 sessions of voluntary motor training facilitated by scES, which included trunk and lower limb extension and flexion. Individuals were assessed of spirometric outcomes, airway pressure generation, and sEMG activity after termination of each training protocol. Participants demonstrated increases in sEMG magnitude and PE_{max} generation after

scES that were sustained after introduction of voluntary training with scES. Two participants demonstrated increases in FVC and FEV_1 with concurrent increases in magnitude of sEMG activity during these events. These results demonstrate that scES has the potential to facilitate functional remodeling within the spinal cord that results in greater respiratory muscle activity during forced breathing and greater respiratory functional capacity, which could potentially lead to novel therapeutic options to improve overall health and quality of life of persons with SCI.

Disclosures: B. Ditterline: None. **S.C. Aslan:** None. **C.A. Angeli:** None. **S.J. Harkema:** None. **A.V. Ovechkin:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Leona M and Harry B Helmsley Charitable Trust

Kentucky Spinal Cord Injury Research Center

University of Louisville Foundation

Title: Task specific spinal cord epidural stimulation enables independent step cycles during BWST stepping in motor complete humans

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Abstract: Various studies in the animal model have shown recovery of stepping with spinal cord epidural stimulation following a spinal cord injury. Our group had shown that epidural stimulation of lumbosacral spinal cord, combined with activity based training, enabled four motor complete paraplegics to progressively regain full weight bearing standing and achieve voluntary movement of their lower extremities.

The objective of this study is to determine whether task-specific epidural stimulation in combination with intense step training can recover independent stepping on a treadmill with partial weight bearing in subjects with a motor complete injury.
Three individuals with a motor complete injury (2 AIS-B and 1 AIS-A) implanted with an epidural electrode array over the L1-S1 segments of the spinal cord participated in this study. Individuals received intense step training with step scES and stand training with stand-scES for 160 sessions. EMG, kinematics and ground reaction forces were recorded during stepping on a treadmill with body weight support.
All three individuals were able to independently generate a full step cycle (stance and swing) with optimized subject specific stimulation parameters for stepping following 20-60 training sessions. The maximum number of consecutive steps generated by the three subjects were 94, 319 and 381 steps. Intention to step with a specific leg (left or right) was needed for independent stepping of that same leg to occur. Although both left and right legs of a given subject could generate independent stepping cycles, neither of the subjects could step bilaterally, simultaneously. These results have important implications with respect to identifying strategies that are likely to be most efficacious in enabling improved motor function for stepping after motor complete paralysis. This study provides evidence that the combination of intense step training with task-specific Step-scES promotes significant plasticity in the spinal circuitry leading to improvements in stepping performance.

Disclosures: C.A. Angeli: None. **Y. Gerasimenko:** None. **V. Edgerton:** None. **S.J. Harkema:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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Topic: C.09. Brain Injury and Trauma

Support: NIH R01EB007615

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Leona M. and Harry B. Helmsley Charitable Trust

Kessler Foundation

Medtronic Inc

Title: Interleaving stand-step training with spinal cord epidural stimulation effectively improved standing in individuals with chronic complete spinal cord injury

Authors: *E. REJC, C. ANGELI, S. HARKEMA
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Abstract: We have recently shown that approximately 80 sessions of stand training with spinal cord epidural stimulation (scES) optimized for standing promoted standing ability improvements in four individuals with chronic complete spinal cord injury (SCI). In particular, two individuals were able to stand without any external assistance, while other two individuals needed assistance for hip extension. Also, all individuals assisted balance with their upper limbs. Interestingly, 80 sessions of step training performed after stand training remarkably impaired standing in three of these four participants. These findings led us to investigate whether standing and stepping can be concurrently trained without limiting the recovery of standing in individuals with chronic complete SCI using scES. In particular, this study examined the effects of an interleaving stand-step training with scES on motor function for standing in three individuals with chronic complete SCI. Stand training and step training alternated every session, and the total number of training sessions remained the same as in the previous protocol (N=160). During this training paradigm we also were more focused on increasing the volitional involvement of the participant, and allowed longer seated rest (up to 30 minutes per session).After approximately 80 sessions of stand-step training, the ability to stand without external assistance was observed in all 3 individuals, for up to 11.4 minutes within a 60-minute standing session. After 160 sessions of stand-step training, standing time without external assistance further increased in all participants (up to 60 minutes within a 60-minute session). Throughout training, participants were also able to stand using less stable upper limb supports (from a standing frame to a walker as well as holding the hands of a trainer). Standing ability improvements were accompanied by adaptations in muscle activation pattern. For example, training promoted less variable electromyographic patterns during standing, and generally increased the evoked potentials amplitude modulation induced by the sit-to-stand transition.In conclusion, the interleaving stand-step training with scES performed in this study promoted significant recovery of standing ability in three chronic complete SCI individuals, and seemed more effective than the previous paradigm in which stand training was completed prior to step training. This indicates that the human spinal circuitry can learn standing while also stepping, as long as standing is practiced. These findings also underline the importance of task-specificity in driving training-induced plasticity of spinal neural networks.

Disclosures: E. Rejc: None. **C. angeli:** None. **S. Harkema:** None.

Poster

053. Spinal Cord Injury: Recovery and Repair

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NIBIB

Kessler Foundation

Kentucky Spinal Cord Injury Research Center

University of Louisville Foundation

Title: Effects of non-task-specific spinal cord epidural stimulation parameters on modulation of leg muscle activity during stepping

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Abstract: Spinal cord epidural stimulation (scES) is one of the most promising neurorehabilitation interventions for individuals with chronic spinal cord injury (SCI). While recovery of stepping is a prominent therapeutic goal of scES, little is known about optimal stimulation parameters to promote recovery of stepping in individuals with SCI. Thus, our aim is to characterize how changes in stimulation parameters, including cathode placement, frequency and voltage, modulate patterns of rhythmic muscle activity during stepping on body weight-supported treadmill with manual facilitation using non-task-specific wide-field scES in individuals with motor-complete SCI. A retrospective analyses of bilateral leg muscle electromyography (EMG) acquired on 6 individuals with SCI were performed. EMGs from each individual included 3 stepping conditions prior to training with scES: stepping without scES, stepping with rostral cathode scES and stepping with caudal cathode scES. Two stimulation voltages were compared through a range of frequencies (5-60 Hz). Left and right leg muscles were analyzed separately to assess interlimb differences within and between individuals. To characterize how changes in stimulation parameters modulate muscle activity during stepping, EMG amplitudes during stance and swing phases were compared 1) across different frequencies at a constant voltage, 2) across different cathode placements at a constant frequency, and 3) between low and high voltages in rostral and caudal cathode placement. The relationships between EMG amplitudes of muscles in the proximal and distal leg segments were also compared to characterize the coordination of antagonistic muscles during stepping in relation to the changes in scES parameters. Results indicated that changes in scES cathode placement, stimulus frequency and voltage differently modulated rhythmic motor patterns during stepping across muscles and individuals. In most individuals, changes in frequency similarly modulated EMG amplitudes both during stance and swing phases. However, in 2 individuals, changes in frequency selectively modulated EMG amplitudes during stance or swing phase, indicating that scES may strongly interact with the step-related sensory inputs. Rostral cathode configuration

tended to generate greater EMG amplitudes in the proximal leg muscles, whereas caudal cathode configuration generated greater EMG in the distal leg muscles. Our findings highlight how pattern generation of human spinal locomotor circuitry, in combination with step-related sensory inputs, can be selectively modulated by varying the epidural stimulation parameters.

Disclosures: S. Sun: None. **S.J. Harkema:** None. **C.A. Angeli:** None.

Poster

054. Trigeminal Processing

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 054.01/Z6

Topic: D.03. Somatosensation: Pain

Support: NRF-2017R1A2B2003561

Title: Quantitative analysis of axons expressing parvalbumin, calbindin, calretinin, stage-specific embryonic antigen-4 and RT97 in the sensory root of the rat trigeminal ganglion

Authors: J. BAE, H. HAN, Y. KIM, J. KIM, *Y. CHO, Y. BAE
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Abstract: Parvalbumin (PV), calbindin (CB), calretinin (CR), stage-specific embryonic antigen-4 (SSEA-4) and RT 97 (phosphorylated NF200) are commonly used as markers for neurons with myelinated fibers or with large myelinated Aβ fibers. To study the selectivity these markers for A myelinated neurons, we analyzed their expression in neurons and axons in the rat trigeminal ganglion by light- and electron-microscopic immunohistochemistry. Most (98.1%) of the RT97-immunopositive (+) fibers and all (100%) the CB+, CR+ and SSEA-4+ fibers were myelinated: Fraction of PV+ small myelinated Aδ (<20 μm^2 in cross-sectional area, equivalent to <5 μm in diameter) and large myelinated Aβ fibers (>20 μm^2 in cross-sectional area, equivalent to <5 μm in diameter) were similar (about 50%). Whereas majority of CB+ (86%) and SSEA-4+ (64%) fibers were small myelinated Aδ fibers, majority of CR+ fibers (86%) were large myelinated Aβ fibers. Majority (62%) of RT97+ fibers were myelinated, but large fraction (38%) were unmyelinated. These findings suggest that PV, CB, CR and SSEA-4 can be used as reliable markers for neurons with myelinated fibers, but not for neurons with large myelinated Aβ fibers, and question the suitability of RT97 as a marker for neurons with myelinated fibers.

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Poster

054. Trigeminal Processing

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 054.02/Z7

Topic: D.03. Somatosensation: Pain

Support: Miyaya Research Grant in A

Title: Surgically induced pain increases orofacial sensorimotor excitability during sleep

Authors: *K. ADACHI[1], R. ODAI-IDE[2], G. J. LAVIGNE[3], B. J. SESSLE[4]
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Abstract: Recently it has been reported that slow-wave sleep disturbance may be induced by inflammation, neuropathic pain and postoperative pain. This finding suggests that the post-operative damage may affect the activity of the trigeminal sensorimotor system across the sleep/awake cycle. The *aim* of the present study was to determine whether jaw-opening reflex (JOR) excitability as well as sleep quality are altered in the postoperative period.
Six-week-old male SD rats (n = 7) received wire implantations, under isoflurane general anesthesia, for recording of the JOR by monitoring the electromyographic (EMG) activities of the bilateral anterior digastric (AD) and masseter (MA) muscles and for electrocardiographic (EKG), electroencephalographic (EEG) and electrooculographic (EOG) recordings. The rats were allowed to recover from the surgical procedure and habituate to the observation environment for a week. Two recording sessions were carried out at postoperative days 7 (D7) and 13 (D13). Sleep-related electrophysiological features (e.g., EMG, EOG, EEG and EKG) were scored with epochs of 4 sec and standardized with those obtained at quiet awake before sleep (QWBS) in each animal. During QWBS, the tongue was stimulated (200 μs) to define the threshold for inducing the JOR in three stimulation trials separated by more than 5 min intervals. Then the animal was allowed to sleep freely and the JOR threshold was determined three times during quiet sleep (QS). The threshold for inducing the JOR during sleep at D7 was significantly ($P < 0.05$) reduced (82.7 ± 2.4%: down-group) in four out of seven animals and was significantly ($P < 0.05$) increased (112.4 ± 5.5%: up-group) in the remaining animals. At D13, prolongation of the observation period significantly ($P < 0.05$) increased the JOR threshold during QS in both down-group (117.2 ± 2.2%) and up-group (120.4 ± 3.4%). At D7, the distribution pattern of slow-wave delta (δ) EEG activity during QS was significantly ($P < 0.05$) increased in both groups (down-group: 176.7 ± 12.7%; up-group: 138.1 ± 8.2%), but the increase of δ EEG activity in the down-group was significantly ($P < 0.05$) greater than that of the up-group. Like the JOR threshold findings, prolongation of the observation period reduced the differences in δ

EEG activity distribution during QS between the down- and up-groups. The appearance of micro-arousals was reduced at D7 and increased at D13 in the down-group but was maintained at a similar level across the observation period in the up-group. These findings suggest that surgically induced pain may disturb both sleep and orofacial sensorimotor excitability.

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Poster

054. Trigeminal Processing

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 054.03/Z8

Topic: D.03. Somatosensation: Pain

Support: KAKENHI 15K11057

Title: Functional regeneration of the afferent axons following inferior alveolar nerve transection

Authors: *T. SUZUKI[1,3], M. KONDO[2], A. KATAGIRI[2], H. NAGASHIMA[1], N. SUGANO[1], S. SATO[1], K. IWATA[2]
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Abstract: During dental treatment, an accidental nerve injury in the trigeminal nerve sometimes causes severe persistent pain in patients. The inferior alveolar nerve (IAN), branch of the mandibular nerve, transmits thermal, mechanical and nociceptive sensations from the lower jaw to the medulla. The IAN has an intrinsic ability to repair and regenerate after injury, but the details of the regenerative process of individual sensations remain to be elucidated. To clarify this, we developed an IAN complete transection model in mice and evaluated the functional regeneration of injured axon by measuring the reflex threshold to mechanical and heat stimulation of the lower lip. We also measured the extracellular signal-regulated kinase (ERK)-positive neurons in the trigeminal spinal subnucleus caudalis (Vc) following noxious stimulation in the lower lip. Also, we classified TG neurons into two types by the expression of chemical markers; CGRP (a marker of peptidergic neurons), and isolectin B4 (IB4, a marker of non-peptidergic neurons) immunohistochemically. Axotomy-induced hypoalgesia to mechanical stimulation persisted until d7. On d28 after IANX, the decreased mechanical threshold was not recovered completely; however, it was partially recovered on d14. The noxious mechanical stimulation resulted in ERK phosphorylation in a subset of Vc neurons on da14 following IANX, suggesting functional regeneration of the IANX involving mechanosensation. In contrast, the hypoalgesia to heat stimulation was not recovered on d14. Also on d3 after axotomy, CGRP and IB4-immunoreactivities (IR) were significantly decreased in TG, and CGRP but IB4-IR was recovered until d14. Our results suggest that after a nerve transection, the mechanosensory

pathway can regenerate and rewire faster compared to the heat-sensory pathway in the injured afferent axons, and CGRP may be dominantly involved in IANX regeneration processes. The authors declare that this study has no conflicts of interest associated with this presentation.

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Poster

054. Trigeminal Processing

Location: Halls A-C

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Program#/Poster#: 054.04/Z9

Topic: D.03. Somatosensation: Pain

Support: Facial Pain Research Foundation

Title: DREADD-induced pain responding and functional connectivity changes in a rat model of trigeminal pain

Authors: L. M. COLON-PEREZ[1], Y. LEVITES[2], R. M. CAUDLE[5], E. L. ROHRS[3], T. E. GOLDE[6], M. FEBO[4], *J. K. NEUBERT[7]
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Abstract: Changes in large-scale neural connectivity could be potential useful markers for trigeminally-mediated orofacial pain. Unique disorders of the orofacial region, such as trigeminal neuralgia, suggest novel modulatory signaling within the neuraxis from the trigeminal nerve to central processing centers such as the nucleus caudalis, thalamus, and somatosensory cortex. Recent advances in designer receptors exclusively activated by designer drugs (DREADD) along with advances in functional MRI offer a unique opportunity to study this circuitry and topological changes that underlie large-scale network alterations due to facial pain. In this study, we determined how activating and inhibiting DREADDs, delivered via AAV, altered functional connectivity in rats following chronic nerve constriction of the infraorbital nerve. Hairless Sprague Dawley rats (female, 300g), were scanned in a 4.7 Tesla Agilent system. A resting state fMRI dataset was collected at baseline (injected with vehicle, DMSO) and a second scan after 45 minutes of injection of CNO (to activate receptors), in a cohort of rats with: activating DREADDs, and inhibiting DREADDs. A 2-shot spin echo EPI sequence was acquired with acquisition parameters for a total acquisition time of 10 mins (an image was acquired every 2s). Time series fMRI signals were extracted from each region of interest (ROI) based on the atlas-guided seed location (150 total areas). The correlation values of the graphs were thresholded for each subject to create matrices with equal densities (e.g the top 15% correlation values). Network

matrices were normalized by the highest correlation value, such that all matrices had edge weight values ranging from 0 to 1. The networks were quantified with the following graph theory metrics: *node strength* (sum of edge weights), and small worldness (topological organization of high clustering among nodes and short number of edges between any node). Rats with activating DREADDs showed a decrease in the node strength compared to baseline while the inhibiting DREADDs showed an increase in node strength. Meanwhile, the small worldness had an opposite effect, activating DREADDs showed an increase in the small worldness index while inhibiting DREADDs showed a decrease in small worldness. This seems to imply that facial pain induces reorganization changes in connectivity strength and topological organization. Inhibiting DREADDs favors increasing in connectivity at the expense of a more inefficient organization (i.e. reduced small worldness), while activating DREADDs favors the more efficient organization while also reducing brain connectivity.

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Poster

054. Trigeminal Processing

Location: Halls A-C

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Program#/Poster#: 054.05/Z10

Topic: D.03. Somatosensation: Pain

Title: Macrophage in trigeminal ganglion contribute to ectopic orofacial pain following inferior alveolar nerve injury

Authors: *D. BATBOLD[1], M. SHINODA[2], Y. SATOSHI[1], K. IWATA[2]
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Abstract: Aim: Accidental mandibular nerve injury may occur in tooth extraction or implant procedure, causing ectopic orofacial pain on occasion. The exact mechanisms underlying the ectopic orofacial pain following mandibular nerve injury is still unknown. Here, we investigated the possible ectopic orofacial pain mechanisms that interact with macrophages and tumor necrosis factor alpha (TNFα) in trigeminal ganglion (TG) following inferior alveolar nerve transection (IANX). **Methods:** We performed IANX in Sprague-Dawley rats (Male, 160-270 g) under Na pentobarbital anesthesia (50mg/kg, i.p.). Mechanical head-withdrawal threshold (MHWT) in the whisker pad skin ipsilateral to IANX was measured every other day for 15 days. Immunohistochemically, we examined Iba1 expression in TG on day 3 after IANX. Next, we measured the MHWT in the whisker pad skin ipsilateral to IANX following successive intra-ganglion administration of macrophage depletion agent, liposomal clodronate clophosome-A (LCCA). In addition, we measured the TNFα expression in TG on day 3 by

immunohistochemical and Western blot technique. We measured MHWT in the whisker pad skin ipsilateral to IANX following successive intra-ganglion administration of Etanercept, TNFα blocker. Finally, we analyzed the TNF receptor-1 (TNFR1) immunoreactive (IR) cells in TG immunohistochemically on day 3. **Results:** MHWT in the whisker pad skin was significantly reduced, and the number of Iba1-IR cells was significantly increased in TG on day 3 after IANX. LCCA administration significantly suppressed the number of Iba1-IR cells in TG and recovered the decrement of MHWT in the whisker pad skin. TNF-α expression was enhanced in TG on day 3 after IANX, which was depressed by LCCA. The reduced MHWT was recuperated following administration of Etanercept. The TNFR1-IR cells were also increased following IANX. **Conclusion:** These findings suggest that TNFα is expressed in infiltrated macrophages in TG and contributes to the development of ectopic mechanical allodynia in whisker pad skin via TNFR1 following IANX.

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Poster

054. Trigeminal Processing

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Topic: D.03. Somatosensation: Pain

Support: SAF2014-54518-C3-1-R

SAF2014-54518-C3-2-R

Title: Functional properties and somatotopical organization of rat trigeminal neurons innervating ocular and periocular tissues

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Abstract: Functional characterization of primary sensory neurons innervating exposed and non-exposed tissues of the ocular surface, such as cornea, conjunctiva and eyelid borders, is incompletely known. The present work examined their electrophysiological properties and impulse responses evoked by different quality stimuli applied to their receptive field (RF). Anesthetized *Wistar* male rats were placed in a stereotaxic frame and electrical activity of trigeminal ganglion (TG) neurons were recorded extracellularly with a tungsten electrode (0.5-5MΩ) inserted vertically within the ipsilateral TG. Neurons were identified by stimulating eye tissues with a thin wet paintbrush or an ice-cooled metal probe. RF and mechanical threshold (MT) were further determined using von Frey filaments (0.08-3.9 mN). Thermal (21ºC or 50ºC saline drops) and chemical (98% CO_2 gas jets; 100μM menthol; 417-733mOsm NaCl) stimuli,

and electrical pulses (0.1-2ms, 15-60V) were applied on the RF to assess polymodality and conduction velocity (CV), respectively. Recorded units (*n*=147) were grouped according to their RF location as corneal (CO), conjunctival (CJ) or eyelid border (EL) neurons. Units were somatotopically organized within the TG (-2mm lateral, -0.5 to -2.0mm posterior to bregma, lower conjunctival and eyelid more rostral than corneal and upper conjunctival and eyelid neurons). Units were functionally classified as polymodal (PN, n=24), mechanical (MN, n=84) and cold (CN, n=39) neurons. CVs ranged from 1.3-2m/s to 2-24m/s, being faster EL-MN. All three sensory types were found in CO and CJ, while only MN were found in eyelids, some associated to eyelashes. PN from CO (*n*=8) and CJ (*n*=16) fired spontaneously at low frequencies ($\leq$1 imp s^{-1}), becoming excited when mechanical, chemical and heat stimuli were applied to their RF, whose area was larger in CO (2.7±0.9mm^2) than in CJ (1.1±0.1mm^2). MN showed no spontaneous activity and were only recruited with mechanical stimuli, being their MT higher in CJ (0.7±0.2mN, *n*=18) than in CO (0.2±0.05mN; *n*=13) or EL (0.2±0.08mN, *n*=53); moreover, their RF were larger in CO (3.0±1.1mm^2) than in CJ (0.6±0.1mm^2) or EL (1.0±0.1mm^2). CN in CO (*n*=28) and CJ (*n*=11) fired rhythmically (1-15 imp.s^{-1}) at basal temperature, becoming excited to temperature decreases (cooling threshold from -0.1 to -14ºC) and menthol, but silenced to heat stimuli, with some paradoxical response to heat. Hyperosmolar saline activated all cold neurons in CO and 55% in CJ. Neurons innervating ocular and periocular tissues are clustered in defined regions of TG, which may be useful to target the desired groups of TG neurons contributing to innocuous and noxious ocular sensations.

Disclosures: B. Santiago: None. **A. Diaz-Tahoces:** None. **J. Gallar:** None. **C. Belmonte:** None. **M. Acosta:** None.

Poster

054. Trigeminal Processing

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 054.07/Z12

Topic: D.03. Somatosensation: Pain

Support: Faculty of Dentistry, Dental Research Institute

Title: Structural characteristics of glial cells in the orofacial sensorimotor cortex of BXA24 mice: gender differences and effects of molar tooth extraction injury

Authors: T. WATASE[1], D. TANG[2], M. ZANJIR[2], I. YONA[2], P. CHERKAS[2], D. K. LAM[3], M. W. SALTER[4], Z. SELTZER[2], K. TAKAHASHI[5], B. J. SESSLE[6], *L. AVIVI-ARBER[7]
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Abstract: **Background**: The orofacial primary motor cortex (oM) plays a crucial role in sensory-motor integration and control of orofacial motor functions. We have shown that tooth extraction in female mice results, at post-operative day 21, in a significantly increased number of astroglia and increased surface area and volume of astroglial processes in layer 5 of the oM (Watase et al., SFN 2016). **Objective**: Since gender is an important factor when studying neurophysiological systems, the aim was to test for gender differences in the number and 3D morphological features of astroglia in the oM of naïve mice and of mice receiving tooth extraction or sham operation. **Methods**: Under isoflurane general anaesthesia, male and female BXA-24 mice (19 - 24 weeks old) had either extraction of the right maxillary molar teeth or sham operation, and naive mice had no treatment (n=6/group). Mice were fixation-perfused on post-operative day 21. For each mouse, six coronal cryosections (40μm) of the left oM region were immunolabeled with anti-GFAP (astroglial marker) and anti-IBA1 (microglial marker). Whole slides were scanned with an Aperio Scanscope at 20x magnification. CaseViewer and Panoramic software were used to quantify the number of astroglia in selected regions of interests (ROI) in layers 1 (300 x 100 μm^2) and 5 (300 x 300 μm^2) of the left oM. 3D Z-stack images were collected using a spinning disk confocal microscope equipped with 63x/1.3 (water) objective lens; Bitplane Imaris software was used to quantify the volume and morphological features of astroglial processes in ROIs in layers 1 (155 x 75 x 15 μm^3) and 5 (155 x 155 x 15 μm^3) of the left oM. Statistics: ANOVA, *post-hoc* Duncan test; $p<0.05$. **Results**: Naive male mice, as compared with female mice, had a significantly larger number of astroglia and microglia in layer 1 ($p<0.001$, 0.01, respectively). Gender differences were also observed in the morphological features of astroglial processes. In both female and male mice, tooth extraction was associated, 21 days later, with a significantly increased number of astroglia (but not microglia) in oM layer 5 ($p<0.001$, 0.01, respectively). **Conclusions**: These novel findings suggest that astroglia may contribute to gender differences observed in tooth loss-induced oM neuroplasticity. **Significance**: Unveiling mechanisms underlying injury-induced astroglial plasticity is an important step towards the development of personalized treatment approaches to improve orofacial sensorimotor functions following orofacial injury.

Disclosures: T. Watase: None. **D. Tang:** None. **M. Zanjir:** None. **I. Yona:** None. **P. Cherkas:** None. **D.K. Lam:** None. **M.W. Salter:** None. **Z. Seltzer:** None. **K. Takahashi:** None. **B.J. Sessle:** None. **L. Avivi-Arber:** None.

Poster

054. Trigeminal Processing

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Program#/Poster#: 054.08/Z13

Topic: D.03. Somatosensation: Pain

Support: NIH Grant DC011579

Oklahoma Center for the Advancement of Science and Technology Grant HR16-108

Title: Oral somatosensory tuning in multimodal taste-active parabrachial neurons associates with receipt of input from trigeminal fibers of the transient receptor potential vanilloid 1 lineage

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Abstract: Interactions between trigeminal oral somatosensory and gustatory neurons in the brain are discussed to contribute to flavor perception. However, such interactions and supporting mechanisms are poorly defined. Here, we combined optogenetic and electrophysiologic methods to elucidate the involvement of transient receptor potential (TRP) vanilloid 1 (TRPV1) lineage trigeminal fibers with oral somatosensory firing in taste-active neurons of the mouse parabrachial nucleus (PbN). TRPV1-Cre mice were crossed with Ai32 Cre-dependent Channelrhodopsin-2 reporter mice to generate TRPV1-Cre;Ai32 mice, which afford blue light excitation of TRPV1-lineage fibers involved with thermo- and somatosensation. Single-unit electrophysiologic recordings were made from taste- and oral somatosensory-active PbN neurons in anesthetized TRPV1-Cre;Ai32 mice during oral chemical and thermal stimulation and also during application of blue laser light (473 nm) to the trigeminal subnucleus caudalis (Vc), which receives the terminals of TRPV1-lineage trigeminal fibers and houses cells that project trigeminal signals to the PbN. Taste responding (spikes) was indexed using temperature-controlled solutions of (in mM) 100 NaCl, 500 sucrose, 10 quinine, 0.1 cycloheximide, 10 citric acid, and an umami mixture. Somatosensory stimuli included oral temperature (14° and 46°C), 1 mM allyl isothiocyanate (AITC; agonist of TRP ankyrin 1 [TRPA1] and TRPV1), and 1 mM capsaicin (TRPV1). Preliminary analyses of 11 taste-active PbN neurons identified a subpopulation (n = 7) that fired in response to optogenetic pulse excitation of TRPV1-lineage fiber terminals arriving at the Vc, suggesting PbN units can merge taste with somatosensory input originating in the TRPV1-lineage fiber class. Accordingly, a subset of these TRPV1-lineage positive taste cells responded to oral delivery of 14°C, 46°C, capsaicin, and AITC. Further, the aversive bitter tastant cycloheximide and noxious 46°C induced spike firing that was positively correlated in TRPV1-lineage positive (r = +0.51) but not TRPV1-lineage negative (r = +0.03) PbN neurons. Appetitive sucrose induced responses in TRPV1-lineage positive PbN neurons that were positively associated with activity to 14°C (r = +0.94) but not noxious 46°C (r = -0.28). Histology showed TRPV1-lineage positive taste neurons resided in the lateral PbN, implicated for affective processing. These data suggest a hedonic dimension guides the integration of taste with oral somatosensory signals originating in TRPV1-lineage trigeminal fibers in a subset of PbN neurons. Such cells may contribute to trigemino-taste affective processes associated with flavor.

Disclosures: **J. Li:** None. **C. Lemon:** None.

Poster

054. Trigeminal Processing

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Topic: D.03. Somatosensation: Pain

Support: KAKENHI No. 24659916

KAKENHI No. 25293422

Miyata Research Grant-in-Aid (A) 2015 from Meikai University

Title: An intracortical connection among somatosensory areas makes higher complemental processing for orofacial sensation in rat

Authors: *N. MIZOGUCHI, A. MINODA, N. SUDA, K. MURAMOTO
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Abstract: The somatosensory signals are transmitted to the somatosensory cortex via the thalamus, and processed in the well-conserved somatotopic manner. Of them, the somatosense of orofacial region has some differences from those of the other body parts in transmitting their information to the related cortices. It has been reported that the electrical stimulation to the periodontal ligament (PDL), a part of orofacial region, elicited simultaneous activation of the primary (S1), secondary (S2) somatosensory cortices, and the insular oral region (IOR) in rat. However, the physiological relationship between S1 and S2/IOR remains controversial. To address this issue, we performed *in vivo* optical imaging using a voltage-sensitive dye, RH1691, and morphological study.

The optical imaging study demonstrated that the electrical stimulation to the PDL of the mandibular incisor evoked simultaneous neural activation in S1 and S2/IOR. The stimuli to each initial response area in either S1 or S2/IOR elicited the responses in the non-stimulated opposite partner site; i.e., stimulation of the S1 evoked excitation of the S2/IOR, and vice versa. Furthermore, an injection of tetrodotoxin (TTX), a sodium channel blocker, to the cortical region between S1 and S2/IOR attenuated such elicited responses only in the non-stimulated cortical partner site. The result of TTX application indicated that these S1 and S2/IOR regions bi-directionally communicate with each other for the signal processing of PDL sensations.

In addition, morphological study using a retrograde neurotracer, Fluorogold (FG), showed the presence of a bi-directional intracortical connection between the initial response areas in S1 and the S2/IOR. FG-positive cells were scattered not only in the injection site but also in the ipsilateral cortical partner area.

These findings suggest that there is not only a conventional projection from S1 to S2 but also a reverse connection from S2/IOR to S1 as an intracortical signal processing network.

Disclosures: **N. Mizoguchi:** None. **A. Minoda:** None. **N. Suda:** None. **K. Muramoto:** None.

Poster

054. Trigeminal Processing

Location: Halls A-C

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Program#/Poster#: 054.10/Z15

Topic: D.03. Somatosensation: Pain

Support: NIH Grant DE022129

NIH Grant EY08098

Title: Viral induced pain not due to damage peripherally

Authors: L. L. BELLINGER[1], P. KRAMER[1], P. R. KINCHINGTON[2], M. B. YEE[2]
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Abstract: Varicella zoster virus (VZV) infects most people causing Chickenpox. VZV infects cutaneous innervating axons, then transports to the neuronal cell body to undergo replication and later viral latency. But there is no need for ongoing VZV replication in humans as most patients given antiviral acyclovir (which inhibits viral DNA replication) show no improvement in virally induced pain. Previous work suggested viral proteins expression after infection induced a nociceptive response in rats. In this study we asked if infection of the terminals and the associated damage was necessary for VZV induced pain. To address this question Sprague Dawley rats were injected with 65,000 plaque forming units (pfu) in 100 microliters of VZV into the whisker pad or 20,000 pfu of VZV in 0.5 microliters directly into the trigeminal ganglia. Control animals received the same volume of vehicle, which was uninfected MeWo cells. Behavioral measurements (place escape aversion paradigm) were completed weekly starting one week after virus injection. After two weeks the animals were sacrificed. Tissues were collected after sacrifice and analyzed histologically. After whisker pad injection and after trigeminal ganglia injection the nociceptive response significantly increased in VZV injected animals versus the controls. After whisker pad injection neurites in this tissue retracted indicating damage to the nerves in the periphery but no retraction or damage was present in the periphery after injection of the trigeminal ganglia. The results indicate that damage and inflammation at the site of injection is not necessary for the nociceptive response. In conclusion, virus damage at the site of infection is not needed for VZV induced pain and the data is consistent with previous reports that neuronal expression of viral proteins induces the pain response.

Disclosures: **L.L. Bellinger:** None. **P. Kramer:** None. **P.R. Kinchington:** None. **M.B. Yee:** None.

Poster

054. Trigeminal Processing

Location: Halls A-C

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Program#/Poster#: 054.11/Z16

Topic: D.03. Somatosensation: Pain

Support: CONACyT (CVU/Grant#) 770703/612278

PAPIIT IA203117

Title: The role of oxytocin receptors modulating nociception at the level of the trigeminocervical complex

Authors: *J. E. GARCIA-BOLL, G. MARTÍNEZ-LORENZANA, M. CONDÉS-LARA, A. GONZÁLEZ-HERNÁNDEZ
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Abstract: Migraine is a common, disabling, neurovascular headache disorder. Briefly, migraine pathophysiology involves abnormal activation of trigeminocervical complex (TCC) neurons. Recently it has been suggested that oxytocin (OT) (a neuropeptide mainly synthesized in the hypothalamic paraventricular nucleus, PVN) is involved in pain modulation at the level of the spinal dorsal horn (SDH). At this level, oxytocin (OTR) or V1a vasopressin receptors (V1aR) seems to play a key role, but the potential antinociceptive effect at TCC remains unknown. The present study aims to establish the effect of spinal OT (and the receptor involved, OTR or V1aR) on TCC neuronal firing evoked by periorbital electric nociceptive stimulation in the receptive field (RF). This RF is innervated by the first branch of trigeminal nerve.
Using anesthetized male Wistar (280-320 g) rats we performed unitary extracellular recordings of wide dynamic range (WDR) neurons of TCC. The nociceptive neuronal responses were evoked by 20 electrical stimuli in the periorbital area (1ms, 0.5 Hz). The evoked activity was analyzed with post-stimulus time histograms that allowed to characterize the WDR neuronal activity by their response latency: Aδ-fibers (3-32ms) and C-fibers (25-80ms). The antinociceptive effect was evaluated with spinal administration of three different doses of OT (10^{-4} M, 10^{-5} M, 10^{-6} M). We found that OT is able to reduce the TCC neuronal firing in response to periorbital-evoked trigeminal activation. Certainly 10^{-4} M OT presented the most significative antinociceptive effect. Next, using highly selective and specific OTR and V1aR antagonists we found that the receptor involved in the OT-induced antinociception correlate with the spinal activation of OTR rather than V1aR. Indeed, we pretreated the TCC with a selective OTR antagonist L-368,899 (10^{-4} M) and found a complete blockade of the action of OT (10^{-4} M) whereas (on another set of experiments) SR-49059 (10^{-4} M; V1aR antagonist) did not have any effect on the OT-induced antinociception.
Taken together, our study showed that OTR activation by OT on the TCC is able to inhibit the

nociceptive input from the first branch of trigeminal nerve. These results point out a new potential target to treat migraine.

Disclosures: J.E. Garcia-Boll: None. **G. Martínez-Lorenzana:** None. **M. Condés-Lara:** None. **A. González-Hernández:** None.

Poster

054. Trigeminal Processing

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 054.12/Z17

Topic: D.03. Somatosensation: Pain

Support: NIH/NIDCR DE018450

WVSOM Intramural Grant

Title: Glial activation in trigeminal ganglia after masseter muscle acid exposure

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Abstract: Earlier we reported on a model for orofacial pain in which repetitive unilateral injections of acidic saline (pH 4) into jaw muscle elicited persistent bilateral pain that was associated with changes in chewing behavior and with significant increases in the expression of substance P and CGRP, BDNF and ASIC3. These increases were prevented by an inhibitor specific to ASIC3, APETX2. There is evidence of a role for satellite glial cells (SGC) in sensory ganglia in mediating hyperalgesia and allodynia in other persistent pain models. SGC activation may provide a means of signaling between primary neurons within the ganglion and an environment conducive to maintenance of the pain state. The objective of this study was to examine SGC activation in our repetitive acidic saline injection jaw muscle pain model and determine if activation is prevented by blocking ASIC3.
Methods: Female CD-1 mice were repetitively injected with either neutral saline (pH 7, n=5), or acidic saline (pH 4, n=5) into the right masseter separated by five days. Five mice were injected with 10µl of APETX2 in PBS (3nM) into the right masseter just prior to the second acidic saline injection; five mice were used as unmanipulated controls. Seven days after the second injection, the mice were sacrificed, ganglia harvested, snap-frozen, and stored at -80^0 until cryosectioned. 12µm cryosections of right ganglia were immunostained for GFAP, a marker for activated glia, and the neuron marker NeuN. Images were acquired using a Zeiss MRm digital camera and Axiovision software and thresholded to produce binary images. The percent area immunolabeled for GFAP was determined for three sections, 150 µm apart, for each animal.

Results: No significant differences in GFAP immunolabeling were observed among controls, neutral saline-injected, or APETX2 injected. In all, 6% of area evaluated was immunopositive for GFAP. However, significant differences were detected between acidic saline injected and all other groups ($p<0.0.5$). In acidic saline injected ganglia, the percent area immunopositive for GFAP was increased two-fold. Increased GFAP immunolabeling was not only associated with SGC surrounding primary trigeminal afferent neurons in acidic saline injected animals, but also was also observed in Schwann cells associated with nerve fibers within the ganglia.
Conclusions: The results of this study suggest that glia activation may play a role in the initiation and maintenance of persistent pain in our repetitive acidic saline injection model for orofacial pain. Furthermore, this activation appears to be prevented by blocking ASIC3.

Disclosures: J. Morris-Wiman: None. **C.G. Widmer:** None.

Poster

054. Trigeminal Processing

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 054.13/Z18

Topic: D.03. Somatosensation: Pain

Support: Facial Pain Research Foundation

Title: Neuroinflammation in posterior insula is correlated with disease duration in trigeminal neuralgia: A free-water diffusion imaging analysis

Authors: *Q. ZHAO[1], C. SPECTOR[2], J. K. NEUBERT[3], M. DING[4]
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Abstract: Neuroinflammation plays an important role in the induction and maintenance of chronic pain. Quantifying neuroinflammation noninvasively in the human brain, however, remains a challenging problem. Recent studies propose that free-water measurement derived from MRI diffusion data provides an index of neuroinflammation. In this method, diffusion of water molecules in the extracellular space and in the intracellular space is separately modeled, allowing the characterization of both extracellular volume (a marker of neuroinflammation) and tissue abnormalities such as axonal degeneration. Here, we applied free-water analysis to trigeminal neuralgia (TN), a debilitating chronic facial pain disorder. Ten TN patients (6 females) gave written informed consent and enrolled in the study. Five of the patients had prior microvascular decompression (MVD) surgery but pain persisted and the remaining five patients did not have prior MVD surgery. Posterior insular, a key brain region known to mediate pain processing and pain perception, was taken as the neural structure of interest. Analyzing diffusion and T1 MRI structural data, we report the following results. First, free water was higher in the

posterior insula contralateral to the side of pain relative to the ipsilateral posterior insula. Second, the volume of free-water in the contralateral posterior insula was positively correlated with disease duration. No such correlation was observed in the ipsilateral posterior insula. Third, the gray matter volume of the contralateral posterior insula was negatively correlated with free water volume but was not correlated with disease duration. Fourth, for the five patients who had no prior MVD surgery, the above pattern of results still hold, whereas for the five patients who had prior MVD surgery, the association between disease duration and free water volume becomes much weaker. Our findings suggest that (1) free water in posterior insula may provide a useful neuroimaging marker of trigeminal neuralgia, (2) the disorder is more strongly associated with neuroinflammation than tissue loss, and (3) MVD surgery may play a role in disrupting the neuroinflammation process. This work was supported by the Facial Pain Research Foundation.

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Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 055.01/Z19

Topic: D.05. Olfaction and Taste

Support: Brigham Young University, College of Life Sciences, Mentoring Environment Grant

Title: Putative pheromone activated brain activity between male and female young adults

Authors: *L. K. HOBBS[1], N. M. STEVENS[2], K. RICHTER[3], M. ANDERSON[4], P. JOHNSON[5], N. MUNCY[4], C. R. DOXEY[4], H. WANG[6], R. HARTLEY[6], K. DAVIS[3], T. OTTESEN[3], C. B. KIRWAN[4], J. WISCO[3,7]
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Abstract: INTRODUCTION: Previous studies have shown that putative pheromones 4,16-androstadien-3-one (AND) and estra-1,3,5(10),16-tetraen-3-ol (EST) cause activation in the preoptic area/anterior hypothalamus in men and women. A split in the activation patterns of neurally matured male and females has been demonstrated when participants are subject to pheromone stimulation (Savic 2008, Lebel et. al. 2008), but the age dependency of this dichotomy in young adults has not been investigated. METHODS: Twenty-nine young [16 female (21.3+/-0.54; mean yrs+/-SE), 13 male (22.85+/- 0.42)], healthy adults participated in a 3-block design, where participants were exposed to a scent (lavender), a synthetic male pheromone (4,16-androstadien-3β-ol), and a synthetic female pheromone (1,3,5(10),16-Estratetraen-3-ol) via an automated olfactometer. Whole-brain, high-resolution (1.8mm3)

functional data from a Siemens Trio 3T MRI scanner were collected during all blocks. RESULTS: Analyses revealed a main effect of sex by stimulus type in the left anterior cingulate, and further investigation revealed that it was the female's reaction to the estrogen that was driving this effect. Further, females responded more strongly to the estrogen in the right frontal pole. Males responded more strongly than females to the androgen in the right temporal-parietal junction, right dorsal-medial prefrontal cortex (PFC), superior parietal lobule, and anterior superior frontal gyrus. No effect of lavender by sex was discovered, indicating equal olfaction between the sexes. Collapsing for sex, the right inferior temporal sulcus was more active for the estrogen than the androgen. CONCLUSION: The study shows that a sexually dimorphic response to pheromones exists in the olfactory system but not to normal scents such as lavender. These distinct functional differences in activation patterns would be a result of neural development and maturation. Future studies should involve a younger demographic to accurately determine the age at which the olfactory response differentiates between males and females.

Disclosures: L.K. Hobbs: None. **N.M. Stevens:** None. **K. Richter:** None. **M. Anderson:** None. **P. Johnson:** None. **N. Muncy:** None. **C.R. Doxey:** None. **H. Wang:** None. **R. Hartley:** None. **K. Davis:** None. **T. Ottesen:** None. **C.B. Kirwan:** None. **J. Wisco:** None.

Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 055.02/Z20

Topic: D.05. Olfaction and Taste

Support: Swartz Foundation

Title: Understanding the relationship between olfactory perceptual discriminability and glomerular response features

Authors: *W. G. BAST, P. GUPTA, D. ALBEANU
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Abstract: For rodents, the ability to recognize and discriminate particular combinations of volatile compounds is essential for their survival. Mice can easily report the difference between weak, similar odors in rich sensory scenes, even when stronger odorants fluctuate in the background. To date, the neural mechanisms underlying such behavior remain unknown.
To understand the neural basis of odor discrimination we measured and manipulated the activity of the inputs nodes of the olfactory system, the glomeruli. By using widefield optical imaging approaches in conjunction with odor stimulation, we tracked the position of glomeruli and quantified their odor response properties; this allowed us to define different sets of affine and non-affine glomeruli with variable number of components. We aim to determine the relationship

between the discriminability of olfactory stimuli and the similarity of glomerular odor response profiles. We additionally quantified the discriminability of the stimuli with the degree of overlap between different sets of glomeruli, as well as the physical separation of glomeruli on the bulb surface.
Towards this end, and to assess the specificity of photo-stimulation, we expressed red-activatable channelrhodopsin[1] (ReaChR) in all mature olfactory sensory neurons and GCaMP6f in the OB output neurons (OMP-Cre x ReaChR x Thy1GCaMP6f). We used DMD-based patterned illumination to selectively stimulate combinations of glomeruli on the dorsal surface of the bulb with sub-glomerular resolution (~10 μm) and high temporal precision (3 ms) in awake, head-fixed mice. Prior to optogenetic stimulation, using a large odor panel (up to ~100 stimuli), we identified the exact locations of glomeruli, revealing their shapes and response tuning to the odors sampled. We further created glomerular light patterns of known odor response similarity (within the range of our panel) and projected specific glomerular inputs. In a two-alternative forced-choice discrimination task, we systematically relate the similarity of these light patterns to the perceived difference between them. Further using a novel strategy to decouple one-photon patterned photo-stimulation and two-photon imaging across different axial planes, we are monitoring the responses of mitral and tufted (M/T) cells in the deeper layers of the bulb.
References:
1. Lin JY, Knutsen PM, Muller A, Kleinfeld D & Tsien RY. Nature Neuroscience 16, 1499-1508 (2013).

Disclosures: **W.G. Bast:** None. **P. Gupta:** None. **D. Albeanu:** None.

Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: D.05. Olfaction and Taste

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Wellcome Trust Investigator Award (110174/Z/15/Z)

Title: Perception and representation of temporally patterned odour stimuli in the mouse olfactory bulb

Authors: *A. ERSKINE[1,2], T. ACKELS[1], D. DASGUPTA[1], I. FUKUNAGA[1,3], A. T. SCHAEFER[1,2]
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Abstract: Odour transmission in natural environments is largely determined by chaotic, turbulent airflow patterns. Naturally occurring odour plumes therefore exhibit a rich temporal structure in the dynamics of odour concentration change, in contrast to the square-pulse odour stimuli commonly used in a laboratory setting. As turbulence continually affects the structure of an odour plume as it is evolved, these dynamics contain information about the distance an odour plume has travelled as well as its source properties. It has, therefore, been hypothesised that animals could process the temporal dynamics of natural odour plumes in order to navigate and perform odour scene segmentation. We investigated the temporal features of odour plumes that are of potential behavioural salience during odour scene segmentation, finding that proximal odour sources show higher temporal correlations than distant sources in their concentration fluctuation patterns. To test whether mice are capable of using these temporal correlations to determine odour source separation, we developed a high-bandwidth odour delivery device capable of replicating many of the temporal features found in odour plumes. In conjunction with a high-throughput behavioural conditioning system (AutonoMouse) we trained mice (n=36) to discriminate between pairs of odours with opposing temporal correlations. Trained mice were capable of discriminating correlation structure at frequencies well over the sniff rate (>15Hz). The high-throughput nature of these behavioural experiments allowed us to determine the psychophysical limit of perception for temporal correlation between odours, and therefore to define an appropriate stimulus range to investigate olfactory bulb representation of these stimuli. Extracellular unit recordings and Ca^{2+} imaging from mitral/tufted cells both revealed diverging responses to these correlated vs. anti-correlated odour stimuli, as well as a degree of single-cell tuning to the frequency component of the stimulus. We conclude that information on temporal correlations between odours is present in the output neurons of the olfactory bulb. Mice are capable of utilising this information in behaviour, suggesting that perception of temporal features of odour stimuli, even at sub-sniff resolution, may be a mechanism by which animals perform odour scene segmentation. Thus, olfaction is a high bandwidth sense with temporal structure containing information about olfactory space that is indeed accessible to mice.

Disclosures: **A. Erskine:** None. **T. Ackels:** None. **D. Dasgupta:** None. **I. Fukunaga:** None. **A.T. Schaefer:** None.

Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 055.04/Z22

Topic: D.05. Olfaction and Taste

Support: DC014453

Title: Odor mixture representation in the olfactory cortex of awake, behaving mice

Authors: *E. SHTRAHMAN, J. GRIMAUD, V. N. MURTHY
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Abstract: An essential function of the brain is to recognize objects in the environment, to identify food, mates, and predators. Olfactory stimuli from natural objects are complex mixtures of multiple odorant molecules, yet the brain is able to perceive these mixtures as unitary objects. How specific patterns of neuronal activity achieve accurate yet flexible encoding of percepts in behaving animals is largely unknown. Training mice to perform complex object recognition tasks has been a major challenge to understanding how neuronal activity relates to perceptions. We devised a novel odor mixture recognition task and are performing tetrode recordings in the piriform cortex of awake, behaving mice. We have developed a two-alternative forced choice task, in which mice categorize three component odor mixtures as either target (unique mixture) or non-target (286 possible mixtures) odors. During training, non-target mixtures do not share any target odorant components. After mice are proficient (performance >90%), they are tested on a pattern separation task, where a single component within the non-target mixture is replaced with a target component ("probe component"). Mice are then required classify these novel mixtures as target or non-targets. Our preliminary findings indicate that the performance on this pattern separation task varies depending on the identity of the probe component, but mice can learn to correctly reclassify all probe mixtures as non-targets with additional training. We are measuring the neuronal representation of odor mixtures in the mouse piriform cortex during these odor classification tasks, and ongoing work will relate neuronal activity to odor mixture perception.

Disclosures: E. Shtrahman: None. **J. Grimaud:** None. **V.N. Murthy:** None.

Poster

055. Olfactory Processing I

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: D.05. Olfaction and Taste

Support: Kobayashi International Scholarship Foundation

Title: Perception of odor mixture is influenced by the molecular complexity of the odor components

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Abstract: The olfactory perception of stimuli generated by a mixture of odorants often differs from that of its original components; however, the mechanism by which this occurs has not been elucidated yet. To identify the determinants of the difference in olfactory perception between individual odorants and novel mixture-based odorants, our group formerly focused on the role that 'molecular complexity' of the individual odorants played in olfactory perception. Although previous results suggest that the molecular complexity of odorant components may influence olfactory perception of the mixture, our analytical method was not sufficient to arrive at a definitive conclusion. We had originally defined an index evaluating the olfactory perception of odor mixtures based on the odor descriptors from Sigma Aldrich, which is commonly used in psychological experiments, but not in neuroscientific research. In the present study, we reanalyzed our data using a newly constructed index for evaluation of olfactory perception. Subjective olfactory ratings for each odorant were obtained from 14 participants (8 women and 6 men) with normal olfaction, and a new index was defined based on participants' ratings, independent of the Sigma Aldrich database. The 'molecular complexity' of each odorant was defined as the structural complexity score obtained from Pubchem, an open database of chemicals. We categorized odorants into 3 groups based on molecular complexity scores: low (<50), medium (~100), and high (>150). This analysis yielded a result similar to that obtained in our previous study, that is, odor mixtures composed of medium-complexity odorants were perceived as new smells, different from the odorant components. In order to examine the neural mechanism by which this difference in olfactory perception occurred, we determined the number of activated glomeruli in the olfactory bulb in mice using data from Yuji K., *et al*. We then found that large numbers of glomeruli were activated by odorants with medium complexity. Large numbers of activated glomeruli can lead to increased overlap of spatial activation patterns. Together, these results suggest that odor mixtures with medium-complexity components can induce an integrated smell.

Disclosures: M. Hamakawa: None. **K. Tamura:** None. **T. Okamoto:** None.

Poster

055. Olfactory Processing I

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Topic: D.05. Olfaction and Taste

Support: DFG Grant SPP 1392 “Integrative Analysis of Olfaction”

Title: Automated operant olfactory conditioning of group-housed mice

Authors: *J. REINERT[1], A. T. SCHAEFER[2,3], T. KUNER[1]
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Abstract: Despite the staggering increase in specific techniques for generating transgenic mouse lines the behavioural analysis of these strains still relies heavily on manual characterisation of individual animals. Not only is this approach labour intensive but also prone to experimenter-induced variations. Additionally, most tests are conducted on single-housed animals during the daytime - a suboptimal setting for social and nocturnal animals.
In the olfactory system we and others have established odour discrimination as a sensitive measurement of olfactory detection allowing for the precise dissection of highly-controlled molecular perturbations (Abraham et. al 2004, Shimshek et. al 2005, Nunes et. al 2015). Yet with more complex modifications the need for the tightly controlled presentation of complex stimuli has become even more relevant.
To circumvent these limitations, we used an automated operant olfactory conditioning setup that allows for group-housing of large cohorts of animals while simultaneously training these animals on a go/no-go odour discrimination task.
Animals, identified via an implanted RFID-tag, initiate trials themselves allowing for generation of unique training protocols specifically tailored to each animal. Simultaneously we could monitor key additional setup-specific parameters like the licking- and sampling-patterns, air flow, air pressure, temperature and humidity with millisecond precision.
Using this setup we were able to concurrently train up to 25 male mice from different genetic backgrounds and with different ages on our paradigm using multiple pure odours as well as the more complex binary mixtures and dilutions. For instance even completely naïve animals were able to reach our criterion of 95% performance in less than 400 trials (321 ± 43 SEM) for the first utterly novel odour pair and even faster for the subsequent odour pair. Interestingly, we could not observe any difference in performance with varying group size of in the quality of learning between more or less active animals.
Regardless of genetic background or group-size, animals typically reached a performance of

95% correct trials within less than 5 days (1,7 ± 0,4 SEM) and subsequently remained constantly high even over weeks of training using the same odour pair.
In summary, this setup enables automated training of socially housed mice while minimizing experimenter interaction with the animals. Apart from odour discrimination the setup can readily be expanded to encompass additional sensory cues or even serve as a pre-training phase to screen for high performing animals for use in further studies like awake 2P imaging or electrophysiological recordings.

Disclosures: **J. Reinert:** None. **A.T. Schaefer:** None. **T. Kuner:** None.

Poster

055. Olfactory Processing I

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Program#/Poster#: 055.07/Z25

Topic: D.05. Olfaction and Taste

Title: Constructing an olfactory perceptual space and predicting olfactory percepts from molecular structure

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Abstract: Given the structure of a novel molecule, there is still no one who can reliably predict what odor percept that molecule will evoke. The challenge comes both from the difficulty in quantitatively characterizing molecular structure, and the inadequacy of language to fully characterize olfactory perception. Here, we present a novel approach to both problems. First, we avoid explicit characterization of molecular structure by using a similarity score for each molecular pair, derived from comparing the molecular structures directly. We show that this method improves on conventional predictions and need not rely on preexisting knowledge of chemical descriptors. Second, we generate a perceptual space, in which a molecule's location defines its percept. We show that from a molecule's neighbors in this space alone, we are able to reproduce all perceptual descriptors of that molecule. We propose that predicting olfactory percept from structure can be rethought of as predicting a molecule's location in this perceptual space. This provides a framework for understanding and predicting human smell percepts.

Disclosures: **D.R. Kepple:** None. **A. Koulakov:** None.

Poster

055. Olfactory Processing I

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Title: Information-theoretic analysis of natural olfactory landscapes

Authors: *S. D. BOIE[1], E. CONNOR[2], M. MCHUGH[2], J. P. CRIMALDI[2], K. NAGEL[3], B. ERMENTROUT[4], J. D. VICTOR[1]
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Abstract: Many species rely on smell to find food sources or mates. In environments where the odor concentration decreases smoothly with increasing distance from the source, it suffices to follow an increasing gradient. However, odor environments are typically turbulent and intermittent; in such environments, animals are also successful odor navigators, but this chemotactic strategy will fail. In turbulent environments, animals' paths indicate that they make navigation decisions on a timescale that could not be supported by obtaining stable averages of plume concentrations - thus indicating that their navigation strategy relies on statistical decisions. These statistical decisions, in turn, must be based on encoding samples of odor concentration at one or more times and locations.
To understand the features of an odor environment that are useful for navigation, we carried out an information-theoretic analysis of plumes. Specifically, we began by taking measurements of realistic spatiotemporal distributions with planar laser-induced fluorescence measurements of neutrally-buoyant odor surrogates. We sampled these distributions via different coding strategies: a strategy that used all available bits to represent odor intensity at a single location and time, a strategy in which the coding bits were allocated to representing odor intensity at a pair of sensors, and a strategy in which the coding bits were divided among multiple samples in time. We then computed the mutual information between sampling location and coded measurements. When the coding bits were all devoted to representing coding odor intensity at a single location, information rapidly saturated. In contrast, coding odor in two locations does not show this

saturation, nor does coding two or more samples separated in time, for up to 10 consecutive samples. For temporal sampling, the optimal time between samples depends on flow conditions, and is longer for plumes near a ground surface. Additionally, resolving a second sample separated in space provides more information than a second consecutive sample taken at the same location. Overall, these findings indicate the importance of exploration, rather than fine-grained coding of intensity, for olfactory navigation.

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Poster

055. Olfactory Processing I

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Pennsylvania Department of Health's Commonwealth Universal Research Enhancement Program

Title: Diverse navigational strategies used to explore odor landscapes

Authors: *A. LIU[1,2,5], J. HENGENIUS[3], M. MARX[4], K. PATEL[2], C. CHENNUBHOTLA[4], B. ERMENTROUT[3,5], N. N. URBAN[2,1,5]
[1]Ctr. for Neurosci., [2]Dept. of Neurobio., [3]Dept. of Mathematics, [4]Computat. and Systems Biol., Univ. of Pittsburgh, Pittsburgh, PA; [5]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA

Abstract: The ability to sense and traverse through an odor landscape is critical for the survival of many animal species, facilitating behaviors such as prey localization or predator avoidance. Mice, insects, and other animals can navigate odor trails and localize odor sources with high fidelity, a remarkable feat given the complex, variable structure of odor stimuli. Since odorants display vastly different structures and properties depending on medium (e.g.: odor trail on the ground vs an odor plume in air), animals likely change navigation strategies depending on stimulus medium and context. Trail following requires coordination between multiple different behaviors - for example, to navigate an odor trail, mice must first locate the trail and then make perceptual decisions on short timescales to remain on the trail. Different features of the trail, such as continuity, curvature, and changes in odorant concentration, may require changes in

navigational strategies. Here, we use a surface odor-based source finding and trail following task to understand how specific stimulus features influence mouse navigation strategy and success by examining behavioral features such as movement velocity and casting. We trained mice (n=5) to localize randomly placed point sources (odorized crayon spot, 20mm in diameter) in a large arena with no light. We vary source concentration (2%, 1%, 0.1% methyl salicylate by volume) and use both baited and unbaited sources to analyze time to spot, casting strategies, and changes in search movement as a function of distance to spot. Preliminary analyses suggest that odor concentration affects trial success, but not time to spot, with increasing failure to find spot rate as odor concentration decreases from 2% to 1% (21% vs. 31% failure rate, respectively). To examine how different trail features change navigation strategy, we trained mice (n=3) to follow drawn odorant trails in a dark arena. We vary trail shape (zig zag, curved with changing magnitude of path tortuosity, self-intersecting), and trail odor concentration (2%, 1% methyl salicylate by volume) to assess whether mice change strategies to match specific features of the trail. We also examine how behavior changes between the detection and following of the trail. Mice can successfully navigate all trail types, but change behavior at decision points during trail following such as during sharp transitions in trail trajectory (e.g. during a zig zag trail) and at regions of self-trail overlap.

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Poster

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Support: NSF grant 1555880

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Title: Assessment of mouse navigation in a virtual reality odor environment

Authors: *K. L. BAKER[1,2], G. CORONAS-SAMANO[1], M. MCHUGH[3], J. CRIMALDI[3], J. V. VERHAGEN[1,2]
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Abstract: Navigation using odor to locate and identify key resources is essential to an animal's survival. Animals rely on olfactory cues to efficiently and accurately move along an odor plume to find food sources, mates and also to avoid predators. Although several behavioral paradigms

have elucidated mechanisms with which animals can successfully navigate, this remains unclear in mammals. Further, the neural mechanism that underlies these processes are unclear. To study these processes, we have developed a virtual reality odor environment for the controlled presentation of a realistic odor plume directly to the nares of transgenic, olfactory receptor neuron specific, GCaMP6 mice. Mice are head-fixed and allowed to walk on a foam ball. The ball rotation is tracked using an optical mouse and registered by a custom Labview virtual interface (VI). The VI generates a 1x1 meter virtual arena where the odor source and relative start position of the animal can be defined. The VI controls the odor intensity to each individual nare as the animal moves through the virtual odor plume. This plume was established by imaging acetone vapor using planar laser induced fluorescence (PLIF) in a defined flow chamber. Prior to behavioral studies, mice are acclimated to handling and the experimental setup. Animals are then trained to control their movement on the ball to receive a reward upon successful navigation along a linear gradient to an area of high odor concentration. Navigation testing then requires the animals to locate the odor source through a VI controlled plume irrespective of start position and angle to the odor source. Light and wind direction cues are also available to the mouse. Five mice of six acquired the task and located the plume source in the majority of trials. Odor navigation strategies are being explored in relation to uni-/multi-modal cue presence and the odor information presented to each nare. Virtual odor navigation is a powerful new approach to understand the neuro-behavioral and anatomical basis of natural odor navigation.

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Poster

055. Olfactory Processing I

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Topic: D.05. Olfaction and Taste

Support: 1555880

1555862

Title: Mouse navigation to ethologically relevant odors in a complex odor environment

Authors: *A. GUMASTE[1,2], K. L. BAKER[1,2], G. CORONAS-SAMANO[1], M. MCHUGH[3], J. CRIMALDI[3], J. V. VERHAGEN[1,2]
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Abstract: Odor-navigation is crucial for animals to use when locating food, choosing mates, and avoiding predators. Although this form of chemotaxis has been well studied in invertebrates, it remains unclear how mammals search for odor sources. Several previously proposed models for odor navigation (e.g., infotaxis) are effective at source localization, but are not likely to be biologically plausible. Recent studies have shifted their focus to studying how animals navigate through airborne plumes, as opposed to odor trails, and suggest that strategies to locate airborne odor sources may be increasingly complex in the presence of turbulence. Further, in large carnivores in the wild, increased plume turbulence has been shown to impede olfactory-based hunting and foraging. Through studying the effect of odor type and plume statistics on odor-navigation, we can gain further insight into the strategies animals use to navigate complex olfactory environments. In a collaborative effort we use turbulent odor plumes, characterized by Planar Laser Induced Fluorescence (PLIF), in a defined behavioral plume flow box to explore odor-based navigation. To do this, we introduce male c57bl/6 mice to a plume box (1x1m) at a fixed downstream location and quantify upstream navigation, using Noldus Ethovision, to one of three randomized active odor ports, upon which successful navigation yields delivery of a sucrose water reward. In order to limit the use of spatial and other non-odor-related cues, trials are terminated if the animal approaches the wrong odor port. Therefore, animals that are unable to directly navigate to the source of the odor do not receive a reward on that given trial. Using this paradigm, we explored differences in navigation to innate (female urine) versus learned food odor cues (amyl acetate paired with sucrose water). Additionally, we studied how the navigational strategies depend on varying plume statistics, including increased turbulence. We anticipate that this data will provide fundamental new insights into how mice navigate to complex odor sources as found in nature.

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Poster

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Topic: D.05. Olfaction and Taste

Support: NSF Grant 1555916

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Title: Computational models of mouse olfactory trail-following: A comparison with behavioral data

Authors: *J. HENGENIUS[1], A. LIU[2,3,4], M. MARX[5,6], C. S. CHENNUBHOTLA[5,6], N. N. URBAN[3,4,2], B. ERMENTROUT[1,4]
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Abstract: Olfactory stimuli provide animals with vital navigational cues that inform foraging behavior, social interaction, and threat avoidance. However, at relevant spatial scales olfactory environments are dominated by turbulent flow and produce stimuli with high temporal variability. This prevents animals from using simple gradient ascent methods to localize odors. Despite the complexity of olfactory environments, animals demonstrate robust trail-following and source localization behavior. Experimental evidence suggests that mice utilize two types of information when following methyl salicylate (MeS) trails or navigating to MeS point sources: (1) spatial left-right nares concentration comparison and (2) temporal sniff-to-sniff concentration comparison during lateral casting movements. Models provide a means of encapsulating these simple mechanistic hypotheses and testing their predictions against data. To that end, we have developed two dynamic models describing these “binaral” and “casting” strategies.
Here we assess model navigation behavior in a stochastic odor environment representative of turbulent flow. We evaluate model performance (*e.g.*, fraction of trail explored, time to point source) and behavior (*e.g.*, linear and angular velocities, trajectory tortuosity and periodicity). To explore model response to trail stimulus complexity, we vary trail tortuosity, maximum curvature, continuity, self-intersections, and concentrations. To evaluate model response to point stimulus complexity, we vary the number, spatial arrangement, and relative concentrations of points. Finally, we compare performance and behavioral metrics to experimental data. We find that both binaral and casting models perform well on trail-following and localization tasks, quickly acquiring/exploring trails and locating points. However, the models do not equally reproduce experimental mouse behaviors. The casting model better fits trail-following data. Conversely, mice seeking point sources display high inter-trajectory variability, yielding some trajectories better fit by the binaral model and others better fit by the casting model. Neither model successfully reproduces mouse behavior far from odor sources, suggesting mice may use additional strategies for distant odor localization.

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Poster

055. Olfactory Processing I

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Topic: D.05. Olfaction and Taste

Title: Spontaneous rapid odor source localization behavior requires interhemispheric communication

Authors: *J. E. RABELL, K. MUTLU, J. NOUTEL, P. MARTIN DEL OLMO, S. HAESLER
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Abstract: To find food, flee from danger or engage in proper social interactions, rodents rely on the ability to identify and spatially localize airborne chemicals. When monitoring the olfactory environment, rodents spontaneously engage in active olfactory sampling behavior, also referred to as exploratory sniffing. Exploratory sniffing is characterized by stereotypical high frequency respiration, which is also reliably evoked by novel odorant stimuli. To study novelty-induced exploratory sniffing, we developed a novel, non-contact method for measuring respiration by infrared (IR) thermography in a behavioral paradigm, in which novel and familiar stimuli are presented to head-restrained mice. We validated the method by simultaneously performing nasal pressure measurements, and confirmed highly reliable detection of inhalation onsets. We further discovered that mice actively orient their nostrils towards novel, previously unexperienced, smells. In line with the remarkable speed of olfactory processing reported previously, we find that mice initiate their response already within the first sniff after odor onset. Moreover, transecting the anterior commissure (AC) disrupted orienting, indicating the orienting response requires interhemispheric transfer of information. This suggests, mice compare odorant information obtained from the two bilaterally symmetric nostrils to locate the source of the novel odorant. We further demonstrate that asymmetric activation of the anterior olfactory nucleus (AON) is both necessary and sufficient for eliciting orienting responses. These findings support the view that the AON plays an important role in the internostril difference comparison underlying rapid odor source localization.

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Poster

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University of Washington Royalty Research Fund

University of Washington Innovation Award

Graduate Opportunities and Minority Achievement Program Presidential Fellowship

Title: Search strategy determines the impact of sensory cues during odor-guided foraging

Authors: *B. J. JACKSON, G. L. FATIMA, S. OH, D. H. GIRE
Psychology, Univ. of Washington, Seattle, WA

Abstract: Odor-guided searches are notoriously difficult due to the sparse and intermittent nature of odor plumes. However, rodents can adaptively modify their search strategy using internal representations of their dynamic environment. This allows for selecting the optimal strategy for making use of complex sensory cues to increase the effectiveness of odor-guided searches. To investigate this we constructed a large (2.5m x 1m) fully-automated open field arena that allowed us to distribute food pellets at precise locations throughout the arena. To simulate nocturnal conditions Long-Evans rats foraged for sucrose pellets under far red light, which they cannot see, forcing them to rely upon olfactory cues to navigate. Rats were divided into two groups and were either trained on predictable (n=8) or unpredictable (n=4) pellet locations. Within a few days all rats were able to complete the task quicker by decreasing their distance traveled and/or by increasing their velocity. Animals trained on the predictable, fixed condition had an increased number of efficient, stereotyped trajectories that persisted in the absence of pellets. To analyze the phases of search, we sectioned trajectories by distance traveled into sequential 3m bins. Animals trained on fixed distributions had significantly more correlated trajectories during the first and second bins compared to animals trained on random distributions. However, animals trained on fixed distributions were significantly impaired in navigating efficiently towards pellets located in slightly unpredictable areas, whereas animals trained on random distributions were only impaired when navigating to the most unpredictable pellets. Efficient performance recovered for all animals when they were about 40cm away from target pellet locations, suggesting this is the distance at which odor cues offer a directional benefit. Animals were then trained to forage for banana-scented sucrose pellets. When navigating to unpredictable pellets from a medium distance (20-80cm), animals had a significantly narrower angle of approach for banana-scented pellets compared to regular sucrose pellets, consistent with more intense odor cues guiding animals from a greater distance. These results suggest that rats form distinct foraging strategies based on learned probabilities of resource locations. Further, they can adaptively switch strategies during a single foraging bout, changing from a memory-based strategy to a strategy that relies on olfactory cues when resources are in unpredictable locations. Further experiments will seek to elucidate the neural correlates behind this dynamic and adaptive shift in search strategies.

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Poster

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Topic: D.05. Olfaction and Taste

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Title: Spatiotemporal dynamics of human olfactory attention during an odor search task

Authors: *G. ARABKHERADMAND, G. ZHOU, H. JIANG, J. GOTTFRIED, S. SCHUELE, C. ZELANO
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Abstract: The process of sensory perception begins prior to any physical contact with the stimulus. Expectation of a stimulus triggers a predictive pattern in the brain which confers advantages to an organism's survival in complex sensory environments. Previous fMRI studies have found that attention to olfactory contents evokes baseline deviations prior to odor sampling in humans. However, the fMRI signal is slow and does not allow direct recording of local field potential oscillations with precise temporal resolution. In this study, we used intracranial EEG (iEEG) methods to investigate the spectral properties of human olfactory attentional neural signatures in primary olfactory cortex. With this method, we were able to record local field potentials directly from human olfactory brain regions.

We acquired iEEG data from patients who had depth wires surgically implanted into the anterior temporal lobe coinciding with piriform cortex. Patients participated in a simple olfactory search task. Each trial began with the instruction to sniff, followed by the presentation of either odorized air or clean air. Trials were separated by 15 seconds of natural breathing of odorless air. This resulted in 3 conditions: 1. Attended sniffs of odorized air (trials in which the participant detected a smell), 2. Attended sniffs of clean air (trials in which the participant did not detect a smell), and 3. Unattended sniffs of clean air (natural breaths occurring in between trials when the participant was not searching for an odor). By comparing condition 2 with condition 3, we were able to compare breaths of an identical stimulus (clean air) with different attentional focus (olfactory attended or not). By examining the time period prior to inhale onset, we were able to look for attentional effects occurring in the absence of any sniffing and in the absence of any odor, two parameters unrelated to attention which could potentially impact local field potential oscillations.

To compare LFP oscillations prior to inhalation during attended and unattended breaths, we generated power spectrograms of raw LFP data using Hilbert transform method (frequency ranges from 0 to 200 Hz, step: 2 Hz). The power spectrograms (dB) of those conditions were compared using a permutation method and multiple comparisons were corrected with cluster-based method. Initial time-frequency analyses indicate desynchronization of low frequency (high-delta/low-theta) oscillations in piriform cortex just prior to inhale onset in attended trials compared to unattended trials. Our findings show that the brain generates anticipatory neural signatures in piriform cortex in response to the expectation of an odor stimulus.

Disclosures: G. Arabkheradmand: None. **G. Zhou:** None. **H. Jiang:** None. **J. Gottfried:** None. **S. Schuele:** None. **C. Zelano:** None.

Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 055.16/AA2

Topic: D.05. Olfaction and Taste

Support: NIH Grant R00_DC_012803

Title: Sound induced olfactory predictive coding in human piriform cortex

Authors: *G. ZHOU, N. ARORA, H. JIANG, S. SCHUELE, J. A. GOTTFRIED, C. ZELANO
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Abstract: A growing body of evidence supports the idea that predictive coding is a fundamental cognitive mechanism across sensory modalities in the human brain. In the olfactory system, fMRI methods have been used to detect predictive codes in both primary and secondary cortical areas (e.g. piriform and orbitofrontal cortex). However, due to the limited temporal resolution of fMRI, the precise timing of olfactory predictive code generation across olfactory neural networks is unknown. Here we used intracranial electroencephalogry (iEEG) methods to study the spatiotemporal dynamics of olfactory predictive code formation in the human brain. In a cued odor-sampling task, each trial began with an auditory cue (the word ‘rose’ or ‘mint’), after which the odor of pure mint or rose was presented. The subject was then asked to indicate whether the presented odor matched the cue. Sound stimuli were delivered via Matlab using a laptop placed in front of the subject. Preliminary data from 6 patients showed increased theta power following the cue in all areas prior to the presence of any odor in each patient ($P < 0.05$, FDR corrected). Interestingly, the olfactory and orbitofrontal cue-related response was preceded by the theta amplitude increase in language/auditory areas. Furthermore, individual phase locking value analysis indicated a consistent cue-induced increase of coupling between the auditory and olfactory areas. Although preliminary, these data suggest that piriform cortex may play a role in integrating sensory information from other modalities during olfactory predictive coding.

Disclosures: G. Zhou: None. **N. Arora:** None. **H. Jiang:** None. **S. Schuele:** None. **J.A. Gottfried:** None. **C. Zelano:** None.

Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 055.17/AA3

Topic: D.05. Olfaction and Taste

Title: Chlorine induced olfactory hyperhedonia

Authors: *R. SOOD[1], F. KHUMALO[2], A. R. HIRSCH[3]
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Abstract: Introduction: Hyperhedonics, or increase in perceived liking or pleasure from sensory stimuli, has been described with age to the odors of lavender and spearmint (Wang, 2005). Hyperhedonics at varying intensities of the odor of phenylethylamine has not heretofore been described.
Methods: Case: A 19 year old right handed woman presented with a 4 month history of sudden onset of hallucinated smell and taste after swimming in a chlorine treated pool whereupon water infused her nostrils. The phantosmia was an unpleasant, fruity, rotten aroma which was always concurrent with the taste of rotten fruit. The phantom taste was 7/10 in intensity. The smell was always the same aroma but of variable intensity. It would occur daily and usually 6-7/10 in intensity lasting up to many hours. It was worse with exposure to odors like bleach and cleaning products. Ambient aromas would mix with the phantom smell to create a distorted odor. Similarly, food flavor would combine with the phantom smell to create a distorted odor. When phantosmia was present, some odorants had enhanced intensity, more than 150% of normal, including kitchen aromas, bleach, and soap. While the patient admits that smells seem more intense, she denies any enhanced hedonics to odors. She also denied cacosmia and palinosmia.
Results: Chemosensory Testing: in the absence of phantosmia: Olfaction: Pocket Smell Identification Test: 3 (normosmia). Sniff Magnitude Test Ratio: 0.49 (normosmia). Alcohol Sniff Test: 30 (normosmia). Snap Phenylethyl Alcohol Threshold Test: left: greater than -2.0 (anosmia), right -9.0 (hyperosmia). Odor Discrimination/Memory Test: 2 at 10 seconds, 3 at 30 seconds, 4 at 60 seconds, total: 9 (normosmia). Olfactometer Identification Test: left: 18 (normosmia), right: 12 (hyposmia). Suprathreshold Amyl Acetate Odor Hedonic Testing: hyperhedonic at all intensities.
Discussion: Formal testing of odor hedonics demonstrating hyperhedonics at all intensities has never before been reported. The mechanism for such hyperhedonics remains unclear. Abnormal discharge in the orbitofrontal cortex, an area involved in the control of hedonics and liking for smell and taste (Stevenson, 2013), is a possible explanation. This highlights the need for development of formal testing for gustatory and flavor hedonics. Assessment of odor hedonics may indicate individual variation in food preferences which may act to predict secondary effects

for such consumption i.e hyperhedonics towards salt (hypertension), sugar (diabetes) and lipids (obesity). Possibly, this patient has hyperhedonics not just to sensory phenomenon but to everything. Testing for such life hyperhedonics may determine this effect.

Disclosures: R. Sood: None. **F. Khumalo:** None. **A.R. Hirsch:** None.

Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 055.18/AA4

Topic: D.05. Olfaction and Taste

Title: Human repeated pregnancy loss is associated with altered olfaction

Authors: *L. ROZENKRANTZ[1], I. FRUMIN[1], N. RESHEF[1], Y. HOLZMAN[1], R. WEISSGROSS[1], N. SARID[1], H. CARP[2], N. SOBEL[1]
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Abstract: In the Bruce effect, mice miscarry in response to bodily odors emitted from a male who did not father the pregnancy. About 15% of clinically identified human pregnancies end in spontaneous miscarriage. Moreover, about 1% of women experience repeated pregnancy loss (RPL), i.e., two or more consecutive unexplained miscarriages. The reasons for most of these miscarriages remain unknown. Given this statistical backdrop, we hypothesize a Bruce-like effect may underlie a portion of the many unexplained human miscarriages. Considering the ethical limitations to causal investigation of human miscarriage, we set out to characterize olfactory processing in RPL women and controls in an effort to identify any circumstantial support for our hypothesis. We studied 21 couples experiencing RPL and 21 matched control couples. We found that RPL women had significantly better olfaction than controls ($F_{1,40}$=7.87, p=0.008), and that this advantage was significantly greater for putative social chemosignals as opposed to ordinary odors ($F_{1,40}$=6.44, p=0.015). Remarkably, we observed a positive correlation between a women's detection threshold for such a social chemosignal and the number of miscarriages she had experienced (r=0.55, p=0.0096). In turn, despite the added sensitivity in RPL women, we found that control women displayed a pronounced physiological and hormonal response to the body-odor of a strange man in comparison to their spouse's body-odor, yet RPL women failed to produce this physiological reaction (physiology: $F_{2,44}$=3.92, p=0.027; hormonal: $F_{1,34}$=4.49, p=0.042). Finally, using an independent set of raters, we found that the body-odor of men in RPL couples was significantly different from the odor of men in control relationships ($F_{1,150}$=9.75, p=0.002). This finding leads us to speculate that RPL can follow a combination of female and male factors that are somehow reflected in olfactory processing. In this we provide circumstantial support for what may be a Bruce-like effect in humans.

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Poster

055. Olfactory Processing I

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 055.19/AA5

Topic: D.05. Olfaction and Taste

Title: Pathological cranial nerve I adaptation demonstrated on olfactory testing

Authors: *K. A. JANJUA[1], A. R. HIRSCH[2]
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Abstract: Introduction: While olfactory adaptation has been described in normosmics (Dalton, 2000) and hyper-rapid adaptation has been postulated in those with dysfunctional olfaction (Roussos, 2014), objective demonstration of such hyper-rapid adaptation has not heretofore been documented.
Method: Case: A 42-year-old right-handed male, one year prior to presentation, underwent cardiac ablation. One week later he noticed a sudden complete loss of taste and smell, without improvement since onset. He has 10-30 olfactory windows a day, which last for 3 seconds, initially strong, and then gradually disappearing. During these he can clearly identify the aromas that are present. He also describes first taste phenomenon, whereby the first bite of food has a strong taste, which disappears by the fourth bite.
Results: Abnormalities in Neurological Examination: Motor examination: left pronator drift with a left abductor digiti minimi sign. Cerebellar examination: low amplitude high frequency tremor on extension in both upper extremities. Olfactory testing: Anosmia on phenylethyl alcohol threshold: Left (L) > -2.0, Right (R) > -2.0; Brief Smell Identification Test: 3; Olfactometer N-butanol Threshold Test: L = 0.0, R = 1.0; Alcohol
Sniff Test: 0; University of Pennsylvania Smell Identification Test: L = 11, R = 8. Sniff Magnitude Test: Sniff magnitude ratio: 0.92. Sniff-n-Sticks: Threshold: L <1, R <1. Odor Memory Test: 10 sec: 1, 30 sec: 1, 60 sec: 1, total: 3; Suprathreshold Amylacetate Odor Intensity Test: horizontal line. Retronasal Olfaction: Retronasal Smell Index: 1; Other: MRI of Brain with and without infusion: normal.
On the 4-item Pocket Smell Test (PST), he readily identified the first odor, which was chocolate, noting that it was strong. The second odor was correctly identified as strawberry, but was with lesser intensity and less certainty. By the third and fourth odors, he incorrectly identified smoke as garlic and leather as mint and could only guess, detecting no odors at all. Repeat PST, 2 hours later, revealed similar results.

Discussion: While the 4-item PST demonstrated pathological olfactory adaptation, it is probable that a similar finding may be true with other identification tests. Error analysis on these tests, in those with olfactory dysfunction, may reveal a rapid decline in olfactory ability. Even when the total score suggests anosmia, further evaluation of these tests for hyper-rapid adaptation is warranted. Such test response may indicate a subgroup that have intact olfactory pathways, and thus be more likely to respond to therapeutic intervention.

Disclosures: K.A. Janjua: None. **A.R. Hirsch:** None.

Poster

056. Neuronal Cell Types: Classification

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 056.01/AA6

Topic: D.07. Vision

Title: The transcriptional signature of von Economo neurons in human frontoinsular cortex

Authors: *R. D. HODGE[1], J. L. CLOSE[1], T. E. BAKKEN[1], J. T. TING[1], J. A. MILLER[1], B. D. AEVERMANN[2], M. NOVOTNY[2], S. I. SHEHATA[1], P. VENEPALLY[2], K. A. SMITH[1], D. N. TRAN[2], J. MCCORRISON[2], F. DIEZ FUERTES[2], S. M. SUNKIN[1], R. H. SCHEUERMANN[2], R. S. LASKEN[2], E. S. LEIN[1]
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]J. Craig Venter Inst., La Jolla, CA

Abstract: Von Economo neurons (VENs) are projection neurons localized primarily within layer 5b of the anterior cingulate and frontoinsular regions of the cerebral cortex in humans, great apes, and several other large-brained social mammals. VENs represent a morphologically-defined cell type with characteristic spindle-shaped cell body, thick bipolar dendrites with limited branching and a moderate density of spines, and often an axon initial segment that emanates from the side of the cell body. Although the precise functional role of VENs remains unknown, a number of studies have shown that VENs are selectively depleted in neurodegenerative diseases such as fronto-temporal dementia, as well as other neurological disorders. Therefore, further insight into the gene expression signature of VENs could prove impactful towards understanding the etiology of these neurological disorders, and may also provide new hints into the functions of VENs in the brain. To reveal the transcriptomic signature of VENs, we used single nucleus RNA-sequencing to analyze the transcriptomes of >800 nuclei micro-dissected from layer 5 of the frontoinsular cortex in two individual adult human postmortem brain specimens. Isolated nuclei were stained with NeuN to enrich for neurons and single nuclei were captured using fluorescence-activated cell sorting (FACS). Smart-seq2 was used to generate cDNA libraries and samples were sequenced on a HiSeq instrument at a median depth of 14 million reads/sample. Iterative clustering revealed several glutamatergic transcriptomic cell types, including one cluster that expressed a number of marker genes

previously described as being specifically expressed in VENs (e.g. GABRQ, ADRA1A), as well as previously unknown marker genes. We validated the gene expression pattern and laminar distribution of this putative VEN cluster in intact tissue using multiplex fluorescent *in situ* hybridization and contrasted its transcriptomic signature to that of other distinct layer 5b glutamatergic neuron types. Our results reveal novel marker genes of VENs in adult human cortex and suggest that morphologically defined VENs have a discrete transcriptomic signature distinct from that of other glutamatergic cortical neurons.

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Poster

056. Neuronal Cell Types: Classification

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 056.02/AA7

Topic: D.07. Vision

Support: Paul Allen

Title: Characterization of human cortical neurons using an *In vitro* single cell characterization platform

Authors: *J. BERG[1], S. A. SORENSEN[1], J. T. TING[1], C. A. ANASTASSIOU[1], C. COBBS[2], N. DEE[1], S.-L. DING[1], N. W. GOUWENS[1], R. P. GWINN[3], C. D. KEENE[4], A. L. KO[5], C. LEE[1], M. MCGRAW[1], P. R. NICOVICH[1], J. G. OJEMANN[5], L. POTEKHINA[1], S. M. SUNKIN[1], A. SZAFER[1], Z. ZHOU[1], C. KOCH[1], H. ZENG[1], E. LEIN[1]
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Abstract: To understand the complexity of cell types within the human neocortex the Allen Institute for Brain Science has established a robust platform to characterize the morpho-electric properties of neurons in human *ex vivo* brain slices. Through collaboration with local surgeons, overlying cortical tissue from human patients undergoing surgery for deep tumor removal or medial temporal lobe epilepsy is collected and processed into acute brain slices. Whole cell patch clamp recordings (with concurrent biocytin filling) are made from targeted neurons, followed by histological processing, imaging, morphological reconstruction, and computational modeling. Rigorous quality control and standardized electrophysiological stimuli allow us to characterize

the input/output function of each neuron, including automated feature extraction of passive and active properties. Similar standards are applied to human neuron fills: high-fidelity z-stack images are generated, and used to create 3D reconstructions of individual neurons. Morphological features such as branch number and density within each layer are automatically extracted from reconstructions, and used for quantitative analyses of morphological type. The platform has been used to characterize hundreds of human cortical neurons from the temporal cortex. These data will be shared openly (joining > 1000 characterized mouse neurons) as part of the online Allen Cell Types Database. Here we describe the platform and resulting dataset in detail and describe differences seen in excitatory and inhibitory neuron properties across layers of the human temporal cortex.

Disclosures: **J. Berg:** None. **S.A. Sorensen:** None. **J.T. Ting:** None. **C.A. Anastassiou:** None. **C. Cobbs:** None. **N. Dee:** None. **S. Ding:** None. **N.W. Gouwens:** None. **R.P. Gwinn:** None. **C.D. Keene:** None. **A.L. Ko:** None. **C. Lee:** None. **M. McGraw:** None. **P.R. Nicovich:** None. **J.G. Ojemann:** None. **L. Potekhina:** None. **S.M. Sunkin:** None. **A. Szafer:** None. **Z. Zhou:** None. **C. Koch:** None. **H. Zeng:** None. **E. Lein:** None.

Poster

056. Neuronal Cell Types: Classification

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 056.03/AA8

Topic: D.07. Vision

Title: Single nucleus and single cell RNA-sequencing identify equivalent neuronal types in mouse visual cortex

Authors: *J. A. MILLER, T. BAKKEN, R. D. HODGE, Z. YAO, D. BERTAGNOLLI, T. CASPER, N. DEE, J. GOLDY, L. T. GRAY, K. LATHIA, S. PARRY, C. RIMORIN, S. SHEHATA, M. TIEU, K. SMITH, B. TASIC, H. ZENG, E. LEIN
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Abstract: The cellular diversity of the brain is enormous, and over 100 years of efforts to classify cell types on the basis of morphology, electrophysiological properties, connectivity, and other properties remain remarkably incomplete. This is especially true in the human brain, where technical and tissue access limitations present enormous challenges to characterizing its roughly 80 billion neurons. Recent studies in mouse brain using single cell RNA sequencing (scRNA-seq) have identified a diversity of cell types based on gene expression signatures that meets or exceeds the diversity described from other modalities. Adult human cortical neurons are more difficult to dissociate, but recent efforts have established that single nucleus RNA-seq (snRNA-seq) is a viable strategy for identifying cell types in frozen postmortem tissues. The nucleus contains a subset of cellular transcripts, and it is unknown whether sufficient information is

captured to identify the full diversity of transcriptomic cell types. To address this question, we performed a targeted comparison of whole cells and nuclei in layer 5 of mouse primary visual cortex (VISp). 470 nuclei were collected and we identified a matching set of 470 cells processed using scRNA-Seq as part of the Allen Cell Types Database (http://celltypes.brain-map.org/; 8,329 total cells). We find that nuclei contain approximately 20-50% the RNA content of whole cells and detect, on average, 70% as many genes. Interestingly, half of the mapped reads from nuclei map to introns, potentially reflecting novel exons, unspliced transcripts, or intron retention, among other mechanisms. By including intronic reads to quantify gene expression, we identify the same cell types using nuclear and whole cell data, suggesting that snRNA-seq is sufficient for cell type classification.

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Poster

056. Neuronal Cell Types: Classification

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 056.04/AA9

Topic: D.07. Vision

Title: Divergent electrophysiological properties of supragranular pyramidal neurons in the human vs. mouse cerebral cortex

Authors: *B. E. KALMBACH[1], R. DE FRATES[2], P. N. CHONG[2], C. COBBS[3], R. P. GWINN[4], A. L. KO[5,6], J. G. OJEMANN[5,6], E. S. LEIN[2], J. T. TING[2]
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Abstract: The development and gross anatomical organization of the mammalian cerebral cortex is strongly stereotyped across species. While all mammals possess a six- layered cortex comprising diverse neuronal cell types, human cortex has undergone dramatic evolutionary expansion, especially in layer 2/3. Additionally, there are spatial and temporal differences in gene expression and marked differences in individual neuron size. Such differences may in principle give rise to our uniquely human capabilities, but detailed cellular-level mechanistic studies across species are required to provide direct functional evidence regarding conserved vs. divergent properties of neocortical cell types and circuits. We compared the intrinsic membrane

properties of human and mouse supragranular pyramidal neurons using the acute brain slice preparation. We performed whole-cell patch clamp recordings from pyramidal neurons with cell bodies located throughout the complete depth of layers 2 and 3 (depth relative to the pial surface). Deeper pyramidal neurons were more depolarized than superficial neurons in both species, yet excitability was oppositely correlated with laminar depth for mouse vs. human neurons. Input resistance decreased as a function of laminar depth for human neurons, while in mouse the opposite relationship was found. Furthermore, in human neocortex I_h-related membrane properties, including voltage sag, rebound from hyperpolarization and membrane resonance increased as a function of laminar depth. In contrast, these h-related properties were largely absent in mouse L2/3 pyramidal neurons regardless of laminar depth. These data highlight considerable differences in the intrinsic membrane properties of human versus mouse suragranular pyramidal neurons. Additionally, our findings implicate a species-specific role for I_h that is most pronounced in deep L3 pyramidal neurons of human temporal cortex, which may generally represent an important evolutionary adaptation for very large pyramidal neurons in the human neocortex.

Disclosures: **B.E. Kalmbach:** None. **R. de Frates:** None. **P.N. Chong:** None. **C. Cobbs:** None. **R.P. Gwinn:** None. **A.L. Ko:** None. **J.G. Ojemann:** None. **E.S. Lein:** None. **J.T. Ting:** None.

Poster

056. Neuronal Cell Types: Classification

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Topic: D.07. Vision

Support: NIMH Grant U01MH105982

NIH Grant R01EY023173

Title: Single cell transcriptomics reveals pan-cortical GABAergic and region-specific glutamatergic cell types in adult primary visual cortex and anterior lateral motor cortex

Authors: *L. T. GRAY[1], Z. YAO[2], K. SMITH[3], T.-N. NGUYEN[1], E. GARREN[1], D. BERTAGNOLLI[3], J. GOLDY[3], S. VISWANATHAN[10], M. ECONOMO[10], C. RIMORIN[3], K. LATHIA[3], N. SHAPOVALOVA[4], D. HIRSCHSTEIN[4], O. FONG[2], V. MENON[10], J. MILLER[5], T. BAKKEN[5], M. TIEU[3], J. GRAY[3], A. WILLIFORD[6], R. LARSEN[1], P. GROBLEWSKI[6], A. SZAFER[7], N. DEE[8], L. LOOGER[10], K. SVOBODA[10], C. KOCH[9], H. ZENG[3], B. TASIC[3]
[1]Mol. Genet., [2]Modeling, Analysis, and Theory, [3]Structured Sci., [4]Applied Genomics, [5]Human Cell Types, [6]Neurosurg. and Behavior, [7]Information Technol., [8]Tissue Processing, [9]Allen Inst. For Brain Sci., Seattle, WA; [10]Howard Hughes Med. Inst., Ashburn, VA

Abstract: The mouse cortex contains a multitude of cell types segregated into layers and functionally distinct regions. To begin to understand the diversity of cell types across the mouse cortex, we have analyzed >11,000 neurons from the primary visual cortex (VISp), and >8,000 neurons from the anterior lateral motor cortex (ALM) by single-cell RNA-seq. Together, these cortical regions represent distant poles of the cortex (VISp, posterior; ALM, anterior), distinct cortical functions (VISp, visual input processing; ALM, preparatory movement planning), and different laminar structure (VISp, granular; ALM, agranular). In order to be as comprehensive as possible, our sample collection focused on unbiased sampling of pan-neuronal, pan-GABAergic, and pan-glutamatergic Cre-driver mouse lines, which were supplemented with collection from layer or cell class-specific mouse lines where additional diversity was apparent from analysis of the unbiased collection. We used data collected from both cortical regions together to derive a transcriptomic taxonomy of cell types by iterative, bootstrapped weighted gene coexpression network analysis (WGCNA). We define 48 transcriptomic GABAergic cell types shared across both cortical regions, despite their distance from each other in physical and functional space. In contrast, 55 glutamatergic transcriptomic types were largely separated by cortical region: 20 types are found only in VISp and another 13 are >93% VISp cells; 15 types are found only in ALM and another 4 are >98% ALM cells. We confirmed gene expression patterns and cell type distribution by RNA in situ hybridization using RNA scope (Garren et al., poster). In addition, to investigate the correspondence of transcriptomic signatures with other neuronal properties we combined retrograde labeling with scRNA-seq and build exquisitely specific new genetic tools to label chandelier cells. This study establishes, at the highest resolution to date, the transcriptomic taxonomy of cortical cell types from functionally distinct regions of the mouse cortex.

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Poster

056. Neuronal Cell Types: Classification

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Topic: D.07. Vision

Support: NIH Grant U01MH105982

NIH Grant R01EY023173

Allen Institute for Brain Science

Title: Verification of transcriptomic cell type markers and cell type location in mouse visual cortex and anterior lateral motor cortex by RNA *In situ* hybridization

Authors: *E. J. GARREN, T.-N. NGUYEN, K. BICKLEY, L. T. GRAY, Z. YAO, T. T. DAIGLE, H. ZENG, B. TASIC
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The mammalian nervous system is composed of numerous cell types, which are usually defined based on their morphology, connectivity and electrophysiology. Recently, transcriptomic profiling of single cells has emerged as a scalable method for molecular profiling and classification of single cells. We have used single cell RNA sequencing (scRNA-seq) to profile more than 20,000 cells from mouse primary visual cortex (VISp or V1) and anterior lateral region of motor cortex (ALM) in many transgenic Cre lines. We identified more than 100 cell types (see Gray et al. poster), and here use RNAscope to assay mRNA expression for select marker genes *in situ*. This approach enabled confirmation of marker coexpression or mutually exclusive expression derived from our scRNA-seq dataset. It also revealed information about the relative location and abundance of cell types.

Disclosures: E.J. Garren: None. **T. Nguyen:** None. **K. Bickley:** None. **L.T. Gray:** None. **Z. Yao:** None. **T.T. Daigle:** None. **H. Zeng:** None. **B. Tasic:** None.

Poster

056. Neuronal Cell Types: Classification

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 056.07/AA12

Topic: D.07. Vision

Support: Part of the project described was supported by NIH (NIMH/NICHD) Grant U01MH105982

Title: Comprehensive census of human cortical cell types defined by single nucleus RNA-sequencing

Authors: *T. BAKKEN, R. D. HODGE, J. A. MILLER, J. L. CLOSE, Z. YAO, L. T. GRAY, S. I. SHEHATA, T. NGUYEN, J. GOLDY, D. BERTAGNOLLI, C. RIMORIN, K. LATHIA, M. TIEU, J. GRAY, T. CASPER, E. BARKAN, M. KROLL, N. DEE, K. A. SMITH, B. TASIC, H. ZENG, S. M. SUNKIN, C. KOCH, E. S. LEIN
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Abstract: The human cortex is composed of approximately 16 billion neurons that are densely interconnected and have diverse morphology, molecular signatures, and firing properties. Neurons can be grouped into types based on shared features, and these cell types simplify the

description of the cortical circuit and facilitate probing its function. Recent technological advances, including high-throughput transcriptomic profiling of single cells, have led to a refined census of cell types in mouse cortex and a much coarser census in human cortex. In this study, we identify a comprehensive set of human cortical cell types derived from single nucleus RNA-sequencing of over 10,000 nuclei isolated from micro-dissected layers of the middle temporal gyrus of post-mortem adult human cortex. Nuclei were stained for NeuN and captured with fluorescence-activated cell sorting (FACS) to enrich for neurons (NeuN+) while also capturing a minority of non-neuronal (NeuN-) cells. cDNA libraries were generated with SMART-Seq v4, and nuclei were sequenced to a depth of approximately 2 million reads per sample. Iterative clustering of gene expression identified over 50 transcriptomic cell types that were well discriminated by a robust set of marker genes. A subset of cell types were validated and localized within cortical layers by multiplex fluorescence in situ hybridization (FISH). Neuronal types had dramatically different expression patterns, including among functionally relevant groups of genes: ion channels, G-protein-coupled receptors, and synaptic genes. Finally, putative homologous cell types between mouse and human were identified based on shared marker gene expression, although there were also substantial differences between species. These data will enable development of novel genetic tools to target specific transcriptomic types and provide an important step toward a full characterization of human cortical cells.

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Poster

056. Neuronal Cell Types: Classification

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Program#/Poster#: 056.08/AA13

Topic: D.07. Vision

Title: Taxonomy of morpho-electric cell types in adult mouse Primary Visual Cortex

Authors: *S. A. SORENSEN[1], J. BERG[4], N. W. GOUWENS[4], C. LEE[5], K. GODFREY, 98105[1], N. DEE[1], M. MCGRAW[1], P. R. NINCOVICH[1], L. POTEKHINA[1], Z. ZHOU[4], C. ANASTASSIOU[1], J. TING[1], A. SZAFER[1], S. SUNKIN[1], C. KOCH[1], E. LEIN[2], H. ZENG[3]
[2]Human Cell Types, [3]Structured Sci., [1]Allen Inst. for Brain Sci., Seattle, WA; [5]Modeling Analysis and Theory, [4]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Understanding the diversity of cell types in the brain has been an enduring challenge. To create a data-driven morpho-electric classification of neurons of the young, adult mouse

visual cortex, we established a single cell characterization pipeline using patch clamp recordings and biocytin fills in *in vitro* slices. Every aspect of the pipeline, from slice preparation, recording, and stimulation, to staining, imaging, 3D reconstructions, and mapping of cells to a reference atlas, employed highly standardized and quality controlled methodology. Transgenic mice were used to ensure both broad coverage of excitatory and inhibitory classes across all cortical layers, as well as selective targeting of rare cell populations. Intrinsic physiological and morphological properties were measured from over 1000 visual cortical neurons, and quantitative features were used to classify neurons into distinct types by data-driven, unsupervised methods. Based on these data, we provide 1) a public, searchable, downloadable morpho-electric dataset of mouse visual cortical neurons (http://celltypes.brain-map.org/) 2) a systematic, morpho-electric characterization of neurons labeled by many of the major transgenic lines used in the field 3) initial anatomical and electrophysiological correspondence with transcriptomic cell types previously defined using these same transgenic lines (Tasic et al. 2016) and 4) a comprehensive taxonomy of morphologically- and electrophysiologically-defined cell types for adult mouse visual cortex. These data provide the basis for a complete description of the local, cell type-specific circuit in this region of cortex.

Disclosures: **S.A. Sorensen:** None. **J. Berg:** None. **N.W. Gouwens:** None. **C. Lee:** None. **K. Godfrey:** None. **N. Dee:** None. **M. McGraw:** None. **P.R. Nincovich:** None. **L. Potekhina:** None. **Z. Zhou:** None. **C. Anastassiou:** None. **J. Ting:** None. **A. Szafer:** None. **S. Sunkin:** None. **C. Koch:** None. **E. Lein:** None. **H. Zeng:** None.

Poster

056. Neuronal Cell Types: Classification

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Program#/Poster#: 056.09/AA14

Topic: D.07. Vision

Title: Towards a viral reporter toolbox for prospective marking of transcriptomic cell classes/types in human and mouse neocortex

Authors: J. MICH[1], B. P. LEVI[1], J. T. TING[1], A. CETIN[1], B. E. KALMBACH[1], B. M. FALL[1], Z. YAO[1], J. A. MILLER[1], T. E. BAKKEN[1], S. YAO[1], M. T. MORTRUD[1], B. OUELLETTE[1], L. T. GRAY[1], T. N. NGUYEN[1], R. P. GWINN[2], C. COBBS[3], A. L. KO[4,5], B. TASIC[1], H. ZENG[1], E. S. LEIN[1]
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Epilepsy Surgery and Functional Neurosurg., Swedish Neurosci. Institute, Seattle, WA, Seattle, WA; [3]The Ben and Catherine Ivy Ctr. for Advanced Brain Tumor Treatment,, Swedish Neurosci. Inst., Seattle, WA; [4]Dept. of Neurolog. Surgery, Univ. of Washington Sch. of Med., Seattle, WA; [5]Regional Epilepsy Ctr., Harborview Med. Ctr., Seattle, WA

Abstract: Despite the known differences in structure and gene expression of the human and mouse neocortex, it is not yet clear how the cell types and their functional circuitry differ across species. Recently, large-scale single cell transcriptomics efforts at the Allen Institute and elsewhere have begun to chart a molecular taxonomy of neocortical cell types, in both mouse and human.
But to uncover the key functional differences between the human and mouse neocortex, it is essential to understand in what ways these cell types—the principal building blocks of the neocortex—are similar and different from each other on both phenotypic and functional levels. For functional studies of mouse cell classes/types, transgenic tools like Cre drivers and reporters are widely employed and have facilitated remarkable advances, but these tools are species-specific and not applicable for human brain research. As a result, the most comprehensive modern toolbox for genetic labeling does not allow for systematic phenotypic and functional comparison of orthologous mouse and human cell types.
We are filling this unmet need by producing and validating a new generation of viral vectors for prospective, rapid-onset labeling of human and mouse cell classes and types. To build these cell class/type-specific viral tools we are identifying conserved cell class/type-specific genes from large RNA-seq datasets, and at the same time mapping open chromatin regions near these genes by layer- and cell class-specific ATAC-seq. We are cloning hundreds of candidate cis-regulatory elements and screening for those that drive cell type/class-specific expression in both mouse and neurosurgical human neocortex. We will validate the top-performing reporter vectors in adult mouse and human neocortical slice cultures by testing phenotype and function of labeled neuronal populations. This project will allow careful comparison between mouse and human neuronal phenotypes and functions using a well-validated set of viral vector tools. Furthermore, because we are specifically looking at conserved elements, our viral tools will likely label orthologous cell types in other mammalian brains, including but not limited to monkey and rat.

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Poster

056. Neuronal Cell Types: Classification

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Topic: D.07. Vision

Support: NIH Grant 3T32HL110852-04S1

NIH Grant UL1 TR001102

Title: Human Brainbow: Multi-color neuronal labeling in human *Ex vivo* brain slices for high-throughput morphological analysis in health and disease

Authors: *S.-H. SHEU[1], P. ADSTAMONGKONKUL[2], J. T. TING[4], L. HOYO[1], I. BOOTHBY[3], E. LEIN[5], J. W. LICHTMAN[3], D. E. CLAPHAM[6]
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Abstract: Several sophisticated expression strategies for stochastic multi-color labeling of cells *in vivo* have been developed over the past decade and applied to genetically-tractable model organisms such as mouse, fly, and fish. The advantage of multi-color stochastic labeling is the ability to encode a wide array of spectrally unique colors such that many closely spaced cells with highly complex morphologies and interconnectivity can be traced within a defined tissue volume using standard confocal microscopy and digital tracing and reconstruction software. In addition, it potentially enables the analysis of connectivity motifs for numerous neurons of the same morphological type within a given sample. As such, these tools have especially facilitated high-throughput investigations of neuronal morphology and synaptic connectivity in the brain. Recently, improved Brainbow designs were adapted into viral vectors including adeno-associated virus (AAV), which presents new possibilities for applying this technology to other species including humans. We have used this viral Brainbow expression strategy to label living neocortical neurons in human *ex vivo* brain slice cultures. We demonstrate specificity of labeling by combining AAV-Brainbow viruses with viruses encoding Cre recombinase under the control of cell type specific regulatory elements. Furthermore, we have achieved surprisingly rapid and robust transgene expression as early as 2-3 days post-infection, which enables analysis of well-preserved neuronal morphologies with minimal confounding factors of prolonged culture time. Lastly, we provide examples of post-hoc morphological reconstruction from high resolution digital image stacks, and quantitative analysis of morphological features for cell type classification. This methodology could in principle be implemented to systematically characterize the diversity of human neuron types and their local connectivity in both healthy and diseased brain specimens.

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Poster

056. Neuronal Cell Types: Classification

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Topic: D.07. Vision

Support: NIH Grant R37 NS029169

Title: Retinal ganglion cell types differ dramatically in survival and responsiveness to neuroprotective interventions following optic nerve crush

Authors: *N. M. TRAN[1], I. E. WHITNEY[1], K. SHEKHAR[3], Z. HE[4], J. R. SANES[2]
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Abstract: Transection of adult retinal ganglion cell (RGC) axons by optic nerve crush (ONC) results in ~80% loss of RGCs within 2 weeks, but a few persist for months. Several interventions that enhance survival have been identified, though none are fully effective. RGCs are composed of >40 types, distinguished by morphological, molecular and functional criteria. Using specific markers, we recently demonstrated that RGC survival after ONC varies dramatically among types (Duan et al., Neuron, 2015). This result implies the existence of type-specific properties that underlie differences in survival, and raises the possibility that modulating these properties could enhance the resilience of vulnerable cells. What are the properties that determine which RGCs live or die? Here, we address this question in three ways. First, we are expanding our assessment of post-ONC RGC survival using additional markers and high throughput single-cell RNA-seq, working towards a complete inventory of surviving types and their molecular profiles post-ONC. We find that RGC types exhibit a broad range of survival rates (from ~5% to ~85%) at 2 weeks post-ONC. This suggests a stronger association between cell type and survival than previously thought. Second, we are asking which RGCs survive following two previously established neuroprotective interventions: *Pten* conditional knock-out (CKO) and combinatorial *Pten*/*Socs3* double CKO with CNTF overexpression. We find these treatments improve survival overall, but the degree of rescue differs among RGC types. Third, we are using high throughput single-cell RNA-seq to profile the transcriptomes of RGCs shortly after ONC (12-48 hours) to assess how gene expression changes in susceptible and resilient types before the onset of degeneration. By determining the gene expression patterns that correlate with survival, we seek to identify novel targets for intervention. These results demonstrate the type-specific nature of neuronal survival following injury and suggest that the incomplete effectiveness of current interventions could be due to specific requirements of individual types.

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Poster

056. Neuronal Cell Types: Classification

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Topic: D.07. Vision

Support: NIH U01MH105960

Title: A cell atlas of the retina

Authors: *K. SHEKHAR[1,2], I. WHITNEY[2], Y. PENG[2], N. TRAN[2], I. BENHAR[1], D. HERMANN[2], E. MARTERSTECK[2], A. R. REGEV, 02142[1], J. SANES[2]
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Abstract: Molecular characterization and classification of neuronal types is increasingly viewed as essential for understanding the structure, development, function and dysfunction of the nervous system. For example, it enables genetic access; facilitates comparison of results across laboratories; and provides a foundation for seeking alterations in brain disorders. As a starting point, we are applying large-scale single-cell transcriptomic analysis to generate a complete "cell atlas" of the mouse retina, a part of the central nervous system that is highly complex but uniquely accessible to study. Current estimates are that there are 100-150 retinal cell types in vertebrates. An initial proof-of-principle survey of 44,808 mouse retinal cells using Drop-seq, a high-throughput microfluidics-based single-cell transcriptomic method that we co-developed, identified only 39 types (Macosko et al., *Cell*, 2015); much of the heterogeneity was likely masked due to the preponderance of rod photoreceptors (~80% frequency). To circumvent this limitation, we are now using specific labels to isolate the three most heterogeneous classes (bipolar, amacrine and retinal ganglion cells (RGCs)) before transcriptomic profiling. In a study of 27,994 bipolar cells (Shekhar et al., *Cell*, 2016), we developed improved computational approaches and combined FISH with virus-mediated sparse labeling to match molecular with morphological criteria for defining types. We thereby identified all 12 types described previously, and found 3 novel types. We are now advancing these results in several ways: (1) By analyzing transcriptomes of >20,000 adult RGCs using improved computational methods, we have classified, and identified molecular markers for ~50 RGC types. (2) Transcriptomic comparison with RGCs profiled at P5 has provided insights into the maturation of specific cell types. (3) We are conducting a similar classification of RGC types in macaque and zebrafish with the hope of generating a systematic cross-species comparison of neuronal types within a diverse class. (4) Many RGCs die following nerve injury, with some RGC types exhibiting better survival rates than others (Duan et al., *Neuron*, 2015). We are comparing changes in gene expression among types following injury to identify early transcriptional signatures that correlate with, and may underlie, selective resilience.

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Poster

056. Neuronal Cell Types: Classification

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Topic: D.07. Vision

Support: NIH Grant

Brain Research Foundation

Title: Single-nucleus RNA and methylation sequencing reveals genetic and epigenetic differences between neurons in mouse visual cortex that project to different visual areas

Authors: *E. J. KIM, Z. ZHANG, T. ITO-COLE, J. R. NERY, J. R. ECKER, E. M. CALLAWAY
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Abstract: In mammalian neocortex, neurons in multiple areas form intricate and precise connectivity to create networks that mediate perception and cognition. For example, in mouse primary visual cortex (V1), individual cortico-cortical neurons project to distinct higher cortical areas that each carry unique information about higher order visual features. However, it remains unknown how these specialized organizational features are formed and maintained. To test the hypothesis that genetic and epigenetic mechanisms interact to establish distinct cell types with different patterns of cortical inter-areal connectivity, we investigated whether neurons that project to different higher visual areas from mouse V1 differ in their gene expression and/or methylation. We isolated thousands of single nuclei from V1 neurons projecting to two distinct higher visual cortical areas, AL and PM, after in vivo imaging to identify areal borders, retrograde virus injection to label individual neurons with nuclear membrane GFP, and FAC sorting. We then performed single-nucleus methylome and RNA sequencing to characterize and compare genome-wide DNA methylation and gene expression profiles, respectively. Our results from unsupervised clustering show that cortico-cortical neurons projecting to different cortical areas differ in both their gene expression and non-CG methylation patterns. Correspondence between gene expression, DNA methylation and projection targets suggest that epigenetic mechanisms work in concert with activity and experience-dependent rearrangements of connectivity to establish appropriate matching between genetically determined functional specializations and environmentally imposed responses to sensory stimuli.

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Poster

056. Neuronal Cell Types: Classification

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Program#/Poster#: 056.14/AA19

Topic: D.07. Vision

Title: Using high density extracellular recordings to classify spike waveforms in the mouse brain

Authors: *X. JIA[1], J. SIEGLE[1], C. BENNETT[1], S. GALE[1], D. DENMAN[1], C. KOCH[1], S. OLSEN[1,2]
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Abstract: The power of large-scale extracellular recordings (hundreds to thousands of neurons simultaneously) would be strengthened if information about different types of neurons and their functional connectivity could be extracted. Neurons are traditionally defined by their genetic markers, morphology, and intrinsic physiological properties. However, these features are typically measured in vitro. In behaving animals, extracellular waveform has been used to categorize neurons into fast-spiking (FS) and regular-spiking (RS) classes. However, it's unclear whether additional classes can be identified purely on spike waveform. Optogenetics can identify cell types based on selective opsin expression, but this method is typically limited to one cell type at a time. Our understanding of neuronal circuitry would benefit greatly from a reliable method to characterize neurons into more detailed classes.
Making use of the newly developed Neuropixels probe with 384 recording sites at 20 μm site spacing, we analyzed extracellular waveforms captured from 40-80 adjacent sites. The high site density allowed us to extract additional features of each spike, such as spread of the detectable waveform, profile of time-to-peak, and propagation velocity along the probe. Combining these features with standard metrics including width and peak-to-trough ratio allowed us to categorize neurons into more subgroups with unsupervised clustering. We validated our clusters with optogenetic tagging experiments, and found PV+ neurons are FS, but SST+ neurons have more diverse waveform shapes. In addition, we found unique waveform signatures in different brain regions. On average, RS waveforms in the visual cortex initiated in the perisomatic region and propagated in a polarized manner toward the pia, which is consistent with previously suggested backpropagating action potentials. In contrast, for neurons in thalamic nucleus LP, we could not detect polarized spike propagation along the probe even though their waveforms are wider than cortical neurons. Finally, spikes recorded from Purkinje neurons in the cerebellum also showed no polarized propagation (which is consistent with the lack of backpropagating sodium spikes in these cells), but cerebellar neurons had narrower waveforms than LP and cortical neurons. In summary, spike waveforms measured with dense electrode arrays permit classification based on additional spatial-temporal features beyond traditional analysis on waveform shape. This method

has the potential to help draw correspondences between the functional properties of different types of neurons in the context of large-scale extracellular recording.

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Poster

057. Cortical Coding and Oscillations

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 057.01/AA20

Topic: D.07. Vision

Title: Representation of sensory uncertainty in Macaque visual cortex

Authors: *R. L. GORIS[1], K. MEDING[1], O. J. HÉNAFF[2]
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Abstract: Animals must act in a world that cannot be known perfectly. The available sensory information is often too limited to unambiguously determine the properties of the environment. Normative theories of perception therefore emphasize that it is critical to take sensory uncertainty into account when making perceptual inferences. Consistent with these predictions, behavioral studies have shown that sensory uncertainty affects perceptual judgements in a wide variety of tasks. But how sensory uncertainty is represented in neuronal responses is still unclear. We manipulated the reliability of Gaussian orientation signals in two different ways and studied spiking activity of orientation-selective neurons in V1 and V2 of anesthetized macaque monkeys. A model-based analysis of these data concerned with mechanisms of orientation selectivity has been previously published (Goris et al., 2015). Here we report that stimulus reliability is manifested in the response reliability of individual neurons, irrespective of the source of sensory uncertainty. Specifically, we found that reducing stimulus energy and increasing stimulus dispersion both reduce the response signal-to-noise ratio (SNR). These effects did not interact with each other and their magnitude was correlated across neurons, suggesting that response SNR directly reflects stimulus reliability. Further analysis revealed that this is due to changes in both response mean and response variance, the latter effect being most important. Specifically, we found that the magnitude of cross-trial fluctuations in response gain exhibits a systematic dependence on stimulus reliability. We show that this coding scheme allows an optimal decoder of simulated population activity to recover stimulus reliability on a trial-by-trial basis. Together, our findings support a view of the visual cortex in which average response magnitude encodes particular stimulus features while interneuronal variability in response gain encodes the reliability of these features.
Goris, R. L., Simoncelli, E. P. & Movshon, J. A. Origin and function of tuning diversity in macaque visual cortex. Neuron 88, 819-831 (2015).

Disclosures: **R.L. Goris:** None. **K. Meding:** None. **O.J. Hénaff:** None.

Poster

057. Cortical Coding and Oscillations

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The Thousand (Young) Talents Program of China

Title: Dynamics of orientation selectivity and its laminar dependence in macaque V1

Authors: *T. WANG, G. YANG, Y. YANG, Y. LI, W. DAI, D. XING
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Abstract: Orientation selectivity is an emergent property of primary visual cortex (V1). Previous studies have proposed that either broadly-tuned suppression or response nonlinearity (power law) may play important roles for sharpening of cortical selectivity. We ask how the two mechanisms collaborate to sharpen the orientation selectivity in V1. We used a linear array electrode to record neural response simultaneously from multiple cortical depths in V1 of awake macaque monkeys. Stimuli with different orientations flashed 20ms each frame. Dynamic responses was calculated with the reverse correlation method. We found that dynamic responses to stimulus orientations are different cross cortical layers. Based on the response dynamics, we estimate the broadly-tuned suppression and response nonlinearity at different layers, we found that suppression is stronger in input layers, while output layers have largest nonlinearity and highest selectivity. Our results suggest that orientation selectivity is sharpened through multiple stages in V1.

Disclosures: **T. Wang:** None. **G. Yang:** None. **Y. Yang:** None. **Y. Li:** None. **W. Dai:** None. **D. Xing:** None.

Poster

057. Cortical Coding and Oscillations

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Support: National Key Basic Research Program of China 2014CB846101

the Thousand (Young) Talents Program of China

the Fundamental Research Funds for the Central Universities

Title: Black-dominant response in primary visual cortex of awake monkyes

Authors: *Y. YANG[1], T. WANG[1], G. YANG[1], Y. LI[1], W. DAI[1], D. XING[1], C.-I. YEH[2]
[1]Natl. Key Lab. of Cognitive Neurosci., Beijing, China; [2]Natl. Taiwan Univ., Taipei, Taiwan

Abstract: It is a well-known phenomenon that humans' sensitivity to dark luminance is better than to bright luminance. Consistent with perception,EEG recording from human subjects showed stronger response for a dark luminance stimulus than for a white one. Previous studies have found strong black-dominant responses in both anesthetized monkey primary visual cortex (V1) and cat area 17. Whether awake non-human primates also have black dominance in V1 is still unknown. In the present work, we used a linear-array electrode (U-probe) to measure population responses to black and white dots in V1 of awake monkeys when they were doing a fixation task. Consistent with previous work, we find there are strong black-dominant responses in V1. We found that the black-dominant responses in layer 2/3 and 4Cb are stronger than those in magno-dominated layers 4B and 4Cα. We conclude that black-dominance is a general phenomenon in primary visual cortex, but that there is a significant difference in black-dominance between M and P pathways in macaque V1.

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Poster

057. Cortical Coding and Oscillations

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Simons Foundation Pilot Award

Title: Internal global gain modulations but not contrast changes preserve the neural code for direction

Authors: *S. LEE[1], J. PARK[2], S. M. SMIRNAKIS[3,4]
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Abstract: External stimuli are represented by the firing of populations of neurons in neocortex. However, the strength of neuronal responses depends not only on the external stimulus that is presented but also on ubiquitously occurring spontaneous fluctuations of internal inputs. Internal input fluctuations modulate sensory responses strongly, altering firing rates of individual neurons by as much as an order of magnitude, even on repeated presentations of identical stimuli. *This raises the important unresolved question how neural population codes are preserved on the face of such fluctuations of internal input.*
The same question can be asked about external stimulus parameters, which strongly modulate the firing rate of individual neurons. Therefore, we studied whether population codes for direction are preserved under ***1)*** changes in stimulus contrast (external input) and under ***2)*** the spontaneous modulation of internal inputs (internal input).
We performed two-photon calcium imaging in mouse V1 layer 2/3 that expressed GCamP6 and observed responses of neural ensembles to moving oriented-gratings at different contrasts. Surprisingly, we found that the neural code is not preserved between different contrasts. This is because, while the shape of direction tuning function is preserved across contrasts at individual neurons, contrast response-gains are highly heterogeneous across neurons.
To observe whether population codes are preserved across different internal input levels, we partitioned the trials within each stimulus condition based on whether overall population activity level was high or low, and studied whether the code for direction was maintained in the two conditions. In contrast to visual contrast, we found that the population code for direction was largely invariance across the two conditions. This was true, even though changes in internal input caused larger firing rate modulations at the single cell level than the changes in stimulus contrast we employed. The reason for this appears to be that gain responses across cells are highly homogeneous during spontaneous internal input fluctuations, thereby preserving the code.
The principles outlined above have potentially important implications for neural circuit mechanisms of information encoding.

Disclosures: S. Lee: None. **J. Park:** None. **S.M. Smirnakis:** None.

Poster

057. Cortical Coding and Oscillations

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Topic: D.07. Vision

Support: NIH Grant 1R01EY024678-01

IARPA Contract D16PC00007

Title: The geometry of encoding Cartesian vs non-Cartesian stimuli in primary visual cortex

Authors: *S. J. KUHLMAN[1], F. BAQAI[2], J. KAUTTONEN[1], B. JEON[1], T. LEE[3]
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Abstract: Traditionally, V1 neurons have been probed with sinusoidal gratings, also called Cartesian stimuli. However, polar and hyperbolic bases for image space reflect the operators that are closely related to taking derivatives of image with respect to different coordinate systems. These operators are thought to be important for aiding perceptual constancy by compensating for affine transformation of the retinal image that arise from changes in viewpoint and object orientation (Hoffman 1966). These stimulus classes have been used to identify cells in MST in monkeys that are selective to changes in rotation, expansion and contraction, as well as for characterizing receptive field properties of extrastriate V2, V4 neurons. In 1993, David van Essen and Jack Gallant showed that primate extrastriate visual cortex exhibits more selectivity to complex non-Cartesian stimuli than Cartesian stimuli when it comes to tuning preference. These receptive fields are also predicted by machine learning methods — they can be learned from videos involving affine transformation such as rotation, scaling and translation, by both Gated Boltzmann machine (Memisevic and Hinton) and predictive encoding models (Zhao et al). Using two-photon calcium imaging, we can monitor populations of hundreds to thousands of neurons with fewer constraints on our choice of stimuli, and explore how that later selectivity could be preserved from information in early visual areas. There are two non- exclusive hypotheses on how this information could be preserved for readout in specialized higher areas: (1) Neurons already exist in V1 with tuning for these non-Cartesian stimuli. (2) The different classes of stimuli might evoke different priors in the form of functional circuits, which should have a signature revealed by dimensionality reduction analysis. Our population analysis of calcium imaging data collected from 9 imaging session in 7 mice revealed: (1) The two subspaces of neural activity in V1 occupied by non-Cartesian and Cartesian stimuli are quantitatively distinct. (2) This difference cannot be fully explained by feedforward receptive field response, because receptive field models matched to receptive fields recovered by dense m-sequence reverse correlation do not predict distinct subspaces. (3) When characterizing the full response patterns

of V1, it is not sufficient to use the classical stimuli of drifting gratings, because the encoding dictionary used by V1 is richer than previously described.

Disclosures: S.J. Kuhlman: None. **F. Baqai:** None. **J. Kauttonen:** None. **B. Jeon:** None. **T. Lee:** None.

Poster

057. Cortical Coding and Oscillations

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Curci Foundation

IARPA Contract D16PC00007

Title: Stability of orientation and spatial frequency tuning in mouse primary visual cortex

Authors: *B. JEON[1], K. QUICK[2], S. CHASE[3], S. J. KUHLMAN[2]
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Abstract: How stable is tuning in the sensory system? On one hand, one might imagine that the computational circuits in the sensory areas of the brain should have robust and stable representations of sensory stimuli so that sensory information can be reliably processed. On the other hand, the brain possesses remarkable plasticity, allowing sensory learning and the integration of new information. Given these competing pressures, how stable are sensory information processing circuits in primary sensory cortex without any external perturbation? In this study, we investigated the day-to-day stability of tuning in the primary visual cortex (V1) of the mouse. We tracked scores of single neurons over multiple recording sessions spanning days to weeks from EMXcre-CamKIITet-ai93 triple allele mice using two-photon calcium imaging. In each session, we measured the neuronal responses to sinusoidal gratings of various spatial frequencies and orientations in layer 2/3 of V1. To assess tuning stability, we computed the correlation in neural tuning across days. We found that the combined tuning to spatial frequency and orientation as a whole was well correlated across days for each mouse ($r = 0.675 \pm 0.055$). We then asked if either the orientation tuning or spatial frequency tuning was more stable than the other. The median correlation values for both orientation tuning and spatial frequency tuning were larger than 0.6 and comparable to one another. We also examined if frequently studied parameters of orientation tuning were stable by comparing the preferred orientation, orientation selectivity index (OSI), and orientation tuning bandwidth across sessions for each neuron. As expected, the preferred orientation was very stable between sessions ($r = 0.980 \pm 0.024$), and OSI

and bandwidth correlations were all larger than 0.5. In addition to these single neuron measures, we also examined the stability at the population level by comparing the signal and noise correlations across neurons. The average differences between the signal and noise correlation matrices were significantly smaller than the average differences by chance ($P<0.001$). In summary, we find that orientation and spatial frequency tuning are largely stable in the mouse over time. This research sets the stage for future studies that assess whether learning-induced changes in neural tuning are larger than expected from day-to-day variability.

Disclosures: B. Jeon: None. **K. Quick:** None. **S. Chase:** None. **S.J. Kuhlman:** None.

Poster

057. Cortical Coding and Oscillations

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Support: IARPA contract# D16PC00007, Microns Program

Title: Primary visual cortex encodes orientation-invariant attributes of complex images

Authors: *P. L. STAN, J. KAUTTONEN, B. JEON, T. PRIGG, J. BREZINSKY, T. LEE, S. J. KUHLMAN
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Abstract: Roughly one-third of visually responsive excitatory neurons in V1 are broadly tuned for orientation (orientation selectivity index, OSI, calculated as 1-circular variance is ≤ 0.3). While there is strong evidence that the more commonly studied two-thirds of V1 neurons, which are sharply tuned for orientation (for example OSI ≥ 0.44), play a role in edge detection, the role of neurons broadly tuned for orientation remains unclear. We hypothesize that neurons broadly tuned for orientation are important for processing stimuli containing complex features. To examine this, we used large field of view calcium imaging in awake mice to compare the responses of excitatory neurons (upwards of 400 neurons per imaging session, 9 imaging sessions from 7 mice) to classic sinusoidal gratings versus complex stimuli (hyperbolic and spiral stimuli created from hyperbolic and polar coordinate systems) at a range of orientations and spatial frequencies (SF). Using greedy decoding algorithms, we designed tasks to identify ensembles of neurons best at performing edge detection (decoding grating orientation), or orientation- invariant attribute detection of complex stimuli (decoding hyperbolic or spiral SF). We found that the properties of neurons comprising the ensembles best at decoding hyperbolic and spiral SF are distinct from those associated with edge detection (OSI for grating = 0.57, hyperbolic = 0.24, and for spiral = 0.22), with some ensemble neurons having no response to gratings (13-17% of the neurons within the high-accuracy, complex SF ensembles). To identify

the response properties that give rise to high accuracy, we used linear regression analysis and determined properties that were significantly correlated with accuracy (Wilcoxon rank sum test of median fit coefficients) for each task. As expected, decoding accuracy of grating orientation was positively correlated with sharpness of orientation tuning ($p<0.01$) and negatively correlated with sharpness of SF tuning ($p<0.01$). In contrast, decoding of hyperbolic SF was negatively correlated with sharpness of orientation tuning ($p<0.05$) and positively correlated with sharpness of SF tuning ($p<0.01$). Similarly to decoding of hyperbolic SF, decoding of spiral SF was positively correlated with sharpness of SF tuning ($p<0.05$), yet these ensembles were largely non-overlapping (spiral-hyperbolic ensemble overlap=14.4%). In summary, we identified ensembles of neurons useful for encoding orientation-invariant features of complex stimuli at the earliest stages of visual cortical processing. Furthermore, there appears to be specialization in V1 for hyperbolic versus polar coordinate systems.

Disclosures: P.L. Stan: None. **J. Kauttonen:** None. **B. Jeon:** None. **T. Prigg:** None. **J. Brezinsky:** None. **T. Lee:** None. **S.J. Kuhlman:** None.

Poster

057. Cortical Coding and Oscillations

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Topic: D.07. Vision

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New York Stem Cell Foundation

Title: Synaptic mechanisms of feature coding in the visual cortex of awake mice

Authors: *H. ADESNIK
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Abstract: In the primary visual cortex (V1) neurons encode multiple features of visual stimuli including their size, contrast, and orientation. The synaptic and circuit mechanisms that underlie the encoding of size and contrast, particularly in awake animals, are still poorly understood. Excitation (E) and inhibition (I) might maintain a constant balance across stimulus space, or their ratio might change. While a fixed E/I balance could control the gain and timing of neuronal responses but not their tuning, a dynamic E/I ratio could play a critical role in feature coding. Recent theoretical work has proposed that cortical networks operate in a ‘stabilized supra-linear network’, or SSN, which can explain diverse phenomena in V1, and predicts that the E/I balance should decline as stimulus size or contrast increases. Consistent with this notion, whole-cell recordings in L2/3 of awake, behaving mice revealed that the E/I ratio systematically declines

with both increasing size and contrast. Dynamic clamp experiments indicated that the observed balances of E and I are sufficient to reproduce the contrast response and size tuning functions of V1 cortical neurons. Finally, optogenetic suppression of somatostatin (SOM) inhibitory neurons strongly enhanced the E and I underlying size tuning, providing a synaptic mechanism for SOM neurons' role in surround suppression. These data imply that contrast and size tuning result from a combination of a changing E/I balance and the tuning of total synaptic input. Furthermore, they lend the first critical lines of experimental support for the SSN model in awake animals, and suggest that a decreasing E/I ratio with increasing cortical drive could contribute to a wide array of cortical computations.

Disclosures: H. Adesnik: None.

Poster

057. Cortical Coding and Oscillations

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Support: NIH EY011488-17

Max Planck Florida Institute for Neuroscience

Title: Testing a sensory neural basis for perceptual learning and discrimination in the tree shrew visual cortex

Authors: *J. W. SCHUMACHER, M. MCCANN, V. K. HOKE, S. FRELING, D. FITZPATRICK
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Abstract: Neurons in primary sensory regions of neocortex encode stimulus features that are important for representing the external world. As sensory features take on behavioral salience, neural representations at the single cell and population level can be modified to enhance the recognition or discrimination of such features. There are multiple ways in which sensory neurons might contribute to perceptual learning for discrimination. One model suggests that sensory neurons act as a bank of quasi-linear feature detectors that contribute feed-forward input to a downstream decoding region, where learning occurs via a reweighting of inputs. Alternatively, a relative enhancement of sensory neurons encoding salient features could form a basis for enhanced discrimination. We tested these models by chronically recording the response properties of large groups of identified neurons in layer 2/3 of tree shrew primary visual cortex across many weeks of fine orientation discrimination learning and performance. Neurons in V1 layer 2/3 of the tree shrew represent the earliest stage of cortical processing to encode

orientation, but how their columnar orientation maps contribute to fine orientation discrimination learning is unknown. To determine whether the layer 2/3 orientation map is the target of learning-related plasticity, we trained adult tree shrews to perform a simple GO/NO GO discrimination task in conjunction with 2-photon imaging of GCaMP6. Affirmative behavioral responses to a grating stimulus at a trained target orientation yielded liquid rewards, while responding to a distractor orientation caused a timeout or air puff. When animals achieved a criterion level of performance, we increased the difficulty of the task by replacing the NO GO grating with a stimulus more similar in orientation to the target. This allowed us to ask whether the learning of finer orientation discriminations improves neural discrimination performance, and where in the orientation map the corresponding changes in neural responses occurred. In some cases population responses to target orientations demonstrated a shift away from the discrimination boundary following learning, suggesting that neurons in orientation domains that flank the target might be enhanced. This coincides with a perceptual shift in the identity of the target orientation, and is consistent with previous studies showing that neurons flanking a discrimination boundary convey high discrimination information. Finally, by longitudinally imaging the response properties of many individual neurons over time, we are able to assess how optimal population coding strategies can be adopted at the single cell level.

Disclosures: **J.W. Schumacher:** None. **M. McCann:** None. **V.K. Hoke:** None. **S. Freling:** None. **D. Fitzpatrick:** None.

Poster

057. Cortical Coding and Oscillations

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Support: NIH Grant EY022730

Title: Experience dependent plasticity of cortical attention states

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Abstract: Modulation of sensory processing by attention occurs in part through the regulation of cortical oscillations in sensory cortex. Abnormal development of cortical oscillations is commonly observed in psychiatric disorders, but the developmental factors contributing to the mature expression of cortical oscillations are poorly defined. Here we test the requirement for retinal input and pattern vision in the development of oscillations in primary visual cortex of c57bl/6 mice alternating between movement and quiet rest. To test the role of retinal input, pups

were enucleated at post-natal days P6, P10, P14 and after the critical period for thalamic and cortico- cortical rewiring but before maturation of cortical activity. The role of pattern vision was tested by binocular eye-lid suturing (ES) before eye-opening (EO). Cortical activity was assayed at P20-30, during the critical period for ocular dominance plasticity, P30-40 after the cessation of this critical period, and in adulthood (P60+) by extracellular multi-electrode array recordings. The local field potentials (LFPs) and spiking activity was recorded in the dark, for control and deprived (ES) animals, followed by visual stimulation to the contralateral eye consisting of grey screen alternating with random noise checkerboard. As expected, in control animals, a robust increase in broad-band beta/gamma power accompanied by a decrease in slower (<10Hz) rhythms occurs during motion as early as P20. Narrow-band gamma oscillations were observed by this age, but were not suppressed by visual stimulation contrast until P30. Activity in deprived and enucleated animals was qualitatively similar to control: movement was associated with decreased slow-wave amplitude and increased spike-rates. Preliminary quantification suggests that development of narrow-band gamma oscillations and their amplitude suppression by stimulation contrast is delayed in deprived and absent in enucleated animals. Further quantification will determine the dependence of specific frequency bands on visual experience as well as the timing of firing rate normalization in deprived animals. Our preliminary results suggest that the development of cortical state regulation in mice develops without retinal input or pattern vision, though it may delay this development and modify the expression of specific frequency bands.

Disclosures: P. Riyahi: None. **M.T. Colonnese:** None.

Poster

057. Cortical Coding and Oscillations

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Title: Laminar functional connectivity in mouse V1 is tuned to stimulus size at early latencies

Authors: *G. PLOMP[1], I. LARDERET[1], M. FIORINI[2], L. BUSSE[2]
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Abstract: In primary visual cortex (V1), spatial integration is an elementary process that is likely mediated by a combination of feed-forward relays from LGN, lateral intracortical interactions, and feedback from higher-level areas. While it is known that each of these contributors can target several V1 layers, the necessary coordination of activity across layers

remains poorly understood.
The hallmark of spatial integration is surround suppression: neuronal activity peaks for stimuli covering the classical receptive field, while it is suppressed for stimuli exceeding it. We hypothesized that identifying size-tuned directed functional connections between V1 layers could help better understand how activity is orchestrated during spatial integration.
We used LFPs recorded with linear depth probes in V1 of awake mice that viewed gratings of various sizes and calculated time-varying directed connectivity (multivariate Granger-causality) between the six cortical layers from stimulus onset to 300 ms after. We then used Bayesian model comparison to identify latencies and frequencies where functional connectivity reflected a tuning curve.
We found that driving from L3 to L5 and L1 was best modeled as a surround-suppressed tuning curve in all animals (n=7) between 60 and 100 ms after stimulus onset. The size-tuning was specific for the alpha and beta frequency band and showed that L3 exerted peak driving on L5 and L1 for stimuli spanning 17 and 39 degrees, respectively, and suppressed driving for larger ones (median suppression indices of 0.6 and 0.3). In addition, we found that driving from L4 to L2 in the beta band was briefly tuned for stimulus size at around 50 ms, with peak driving for stimuli of 25 degrees and a suppression index of 0.6.
These findings are a first demonstration that inter-laminar functional connectivity parametrically varies with stimulus size. The results are in line with the notion that L4 relays size-tuned information from LGN to supragranular layers at early latencies, and that supragranular layers then coordinate activity in the column by gating inputs from higher-level areas targeting L5 and L1.

Disclosures: **G. Plomp:** None. **I. Larderet:** None. **M. Fiorini:** None. **L. Busse:** None.

Poster

057. Cortical Coding and Oscillations

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Title: The turtle visual system mediates a complex spatiotemporal transformation of visual stimuli into cortical activity

Authors: *M. HOSEINI[1], J. POBST[2], N. WRIGHT[2], W. CLAWSON[3], W. L. SHEW[3], R. WESSEL[2]
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Abstract: The dorsal cortex of turtle is a three-layered visual cortex that receives non-retinotopic axonal projections from LGN, that is characterized by extensive intracortical axonal projections, and that operates at criticality during visual processing. Together, these observations of circuit anatomy and dynamics raise an important question: What is the spatiotemporal organization of visual responses in turtle visual cortex?
To address this question, we employed the turtle eye-attached whole-brain *ex vivo* preparation and inserted microelectrode arrays (MEAs) into the geniculo-recipient dorsal cortex. We thus obtained recordings of extracellular neural activity (LFP and spikes) during visual stimulation of the retina. We quantified the spatiotemporal structure of visual responses. Visual stimuli included diffuse red flashes of light, black dots moving on a white screen and naturalistic movies.
These recordings revealed important features of stimulus-modulated cortical activity: (i) Visual responses to diffuse brief flashes of light were persistent, oscillatory, and outlasted the stimulus by several seconds. Typical response latencies to first evoked spike were around 250 to 500 ms. (ii) When probed with small moving dots, the trial-averaged receptive fields of both LFP and single-unit spiking spanned large areas of the visual field, often covering more than half of the visual field. Nevertheless, the large receptive fields were not homogeneous, rather receptive fields consisted of site-specific shape and internal structure. The similarity of receptive fields of two recordings sites decreased with increasing spatial separation. We found no evidence for directional tuning. (iii) The effects of adaptation were clear, long lasting, and ubiquitous. Both previous visual stimuli and previous cortical activity triggered adaptation. Responses to visual stimulation of one area of the visual field caused adapted responses to visual stimulation in another area of the visual field. (iv) Response variability to repeated presentations of identical stimuli was large and manifested itself in different ways. Responses varied in strength, were all or none, or varied in their temporal and spectral properties.
In conclusion, these results demonstrate complex spatiotemporal transformations of visual stimuli into cortical activity that, at present, largely evade computational frameworks.

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Poster

057. Cortical Coding and Oscillations

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Title: Possible contribution of retinotopic-scale luminance signals in primate V1 to visual pattern discrimination

Authors: *G. BENVENUTI, Y. CHEN, W. S. GEISLER, E. SEIDEMANN
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Abstract: Our visual system is capable of discriminating visual patterns over a wide range of spatial scales. For example, orientation discrimination (OD) thresholds can be less than one degree, and this sensitivity is only modestly affected by changes in spatial frequency (SF) and size over more than two orders of magnitude. What are the neural mechanisms that underlie these remarkable capabilities? Orientation selective V1 neurons are likely to contribute to performance in OD. However, at any location in V1, neurons have a limited range of receptive field sizes. Therefore, when the SF of the stimulus is sufficiently low, V1 neurons should carry little information about the stimulus' orientation. How can we be highly sensitive to orientation at low SFs if individual V1 neurons carry little information about orientation?To address this question, we used voltage-sensitive dye imaging to measure V1 population responses to briefly presented sinusoidal gratings at different orientations and SFs in awake, fixating macaque monkeys. We analyzed V1 responses at the large retinotopic scale and at the fine orientation columns scale. As expected, we found that the strength of orientation selective signals at the columnar scale drops rapidly as the SF of the stimulus is reduced, even though the overall response to low SF gratings remains strong. We then examined responses at the retinotopic scale and discovered a surprising signal that varies with the orientation and phase of low SF gratings (<2 cpd; eccentricity ~3 deg). Each grating elicits spatial modulations of V1 population responses that match the projection of the stimulus' luminance pattern to the retinotopic map. This spatial pattern, which is related to ON/OFF imbalance in V1, carries high quality information about orientation that could contribute to OD at low SFs. Downstream mechanisms that compute orientation based on this retinotopic signal (while ignoring each neuron's orientation preference) could play a key role in discrimination of low SF patterns. Such mechanisms could also explain our ability to discriminate the orientation of large objects created by contrast modulation of fine-scale texture. Our measurements also show that such "second order" patterns are only represented at the retinotopic scale in V1. Overall, our results suggest that two modes of pattern representation co-exist in V1. A representation of features by tuned neurons and columns, and a distributed representation where information is represented by the relative level of activity across a topographic map. An important goal for future research is to determine the contribution of these distributed retinotopic signals to pattern discrimination.

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Poster

057. Cortical Coding and Oscillations

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Support: Boehringer Ingelheim Fonds

Title: Binocular integration and disparity sensitivity in mouse visual cortex

Authors: *A. LA CHIOMA, T. BONHOEFFER, M. HÜBENER
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Abstract: Binocular neurons in the visual cortex combine signals from left and right eye images. The small differences between these images, called binocular disparities, provide the visual system with critical information for depth perception. In primates and cats, individual neurons sensitive to binocular disparities are found in almost all regions of the visual cortex, with somewhat different disparity tuning properties across primary and higher visual areas.
The mouse visual cortex consists of the primary visual area (V1) and more than a dozen extrastriate areas, whose roles in visual information processing are, however, only partly understood. Mouse V1 has been reported to contain disparity-tuned neurons similar to those found in other mammals. However, binocular disparity is still rarely studied in the mouse, and it has not been investigated whether it is differentially represented among higher visual areas. Comparison of disparity tuning across different mouse visual areas might help delineating their functional specialization.
We therefore characterized binocular disparity in V1 and in two higher visual areas, LM and RL. Visual areas were first identified with intrinsic signal imaging, using the established retinotopic organization of these areas. To record the activity of single neurons in the selected regions, we then performed two-photon imaging using the genetically encoded calcium indicator GCaMP6s. To measure disparity tuning, binocular drifting gratings at varying relative interocular phases as well as random dot stereograms were dichoptically presented using a haploscope, allowing for independent stimulation of each eye.
With grating stimuli, we observed that across these areas a large fraction of neurons were modulated by disparity. Of these, only a fraction responded to random dot stereograms, but those which did also showed disparity selectivity. Integration of binocular stimuli generally led to strong response facilitation or suppression at optimal or null disparity, respectively, even in neurons classified as monocular by conventional ocular dominance measurements. We found no evidence for a spatial organization for binocular disparity within the areas, in agreement with the salt-and-pepper organization observed for other response properties in mouse visual cortex. We did observe, however, that neurons with similar disparity tuning had higher noise correlations,

suggesting that they were more strongly interconnected or shared common input. Overall, we find no major differences in disparity tuning and binocular integration across areas V1, LM and RL.

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Poster

057. Cortical Coding and Oscillations

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Support: ANR

Title: Temporal frequency invariance of receptive field width in primate V1 neurons

Authors: *F. E. ROUMIER, M. SEMAMI, J.-B. DURAND, N. PICARD, P. GIRARD, L. NOWAK
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Abstract: It has been proven that stimulus contrast influences the width of the receptive fields (RFs) of V1 neurons. However, the results differ depending on the approach used to measure RF extend: techniques using drifting sine-wave gratings with varying sizes revealed an apparent expansion of the receptive field at low contrast whereas techniques based on static flashing bars (sparse noise) revealed a contraction of the receptive field at low contrast. One possible explanation for this discrepancy resides in the temporal frequency used with these two stimulation techniques, which is relatively low with drifting gratings (around 1-5 Hz) and quite higher with flashed bars (10-50 Hz). In this study we explored the effect of the temporal frequency itself on the amplitude and width of RFs in the primary visual cortex (area V1). We performed extracellular recordings of V1 neurons in anesthetized and paralyzed marmoset monkeys. RFs were mapped using a static bar (brighter or darker than the background) flashed successively and randomly across 16 positions covering the full extent of the receptive field. Stimuli were presented at 4 different temporal frequencies: 2, 5, 10 and 20 Hz. RFs were reconstructed using a forward correlation method. We found that response strength (RF amplitude) was strongly dependent on stimulus temporal frequency: in comparison to that obtained at 2 Hz, the amplitudes of the RFs at 5, 10 and 20 Hz were significantly reduced by 12, 30 and 42%, respectively. Furthermore, 30 % of the cells tested did not respond at 20 Hz while they presented significant responses with lower temporal frequencies. On the other hand, the width of RFs obtained at 2 Hz compared to that obtained at 5 and 10 Hz showed only weak and marginal effect of the temporal frequency (about 10 %) and no effect could be revealed by comparison of the RF maps at 2 Hz and 20 Hz. These results suggest that the temporal frequency

of the stimuli used to map the RFs has a strong influence on response amplitude but no strong effect on RFs width. This implies that RF width is invariant with respect to stimulus temporal frequency. These results also imply that the opposite effect of contrast on receptive extent, depending on whether it is estimated using (low frequency) drifting gratings or (high frequency) flashing bar, is not due to the different temporal frequencies used with the two stimulation techniques.

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Poster

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NSF 1539034

Title: The effects of cortical depth on response properties in mouse V1

Authors: *P. J. O'HERRON, J. WOODWARD, P. KARA
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Abstract: Over the last decade, mice have become a popular model system for studying visual processing, due to the large array of optical and genetic techniques available for recording and manipulating neural activity. In contrast to larger mammals, the greater ease of imaging the small and relatively transparent mouse brain with multi-photon microscopy has further accelerated their use in systems neuroscience. As a result, the response properties of neurons in mouse primary visual cortex (V1) have been well characterized. Studies have consistently found that approximately half of the neurons respond to drifting grating visual stimuli. This percentage of responsive neurons is considerably smaller than the responsiveness found in other species such as cat and monkey, where nearly all neurons are activated by such stimuli. Additionally, the cortical depth of the neurons under study is frequently not considered in calcium imaging studies, and thus the response properties of neurons from cortical layers 1 through 4 are often pooled together for analysis. Here, using two-photon microscopy, we show that as the imaging depth progresses from superficial layer 2 to layer 4, there is a continual and dramatic increase in the percentage of responsive neurons in mouse V1, ultimately reaching levels similar to what is commonly seen in cats and macaque monkeys. This increased responsiveness with cortical depth in mouse V1 is accompanied by an increase in the response amplitude and a moderate decrease

in the orientation selectivity of individual neurons. The change in response properties through depth may be due to differences in the distribution of thalamic inputs terminating in V1. Unlike in cats and monkeys, the thalamic inputs in mouse V1 are not as constrained to layer 4 but ramify extensively into layer 2/3. The density of the inputs increases through layer 2/3 and into layer 4, qualitatively matching the gradient of response properties we see. These results point to the importance of considering neuronal depth in the analysis of visual response properties. Furthermore, the inability to drive the majority of cells in superficial layer 2/3 of mouse V1 with grating stimuli indicates that there may be fundamental differences in the role of V1 between rodents and other mammals.

Disclosures: **P.J. O'Herron:** None. **J. Woodward:** None. **P. Kara:** None.

Poster

057. Cortical Coding and Oscillations

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Wellcome Trust/NIH joint PhD Studentship (100931/Z/13/Z)

Title: Probing binocular computation using nonlinear models of v1 recordings

Authors: ***F. BARTSCH**[1,2], S. HENRIKSEN[3,4], B. G. CUMMING[3], D. A. BUTTS[1,2]
[1]Dept. of Biol., Univ. of Maryland, College Park, MD; [2]Program in Neurosci. and Cognitive Sci., College Park, MD; [3]Natl. Eye Institute, NIH, Bethesda, MD; [4]Inst. of Neuroscience, Newcastle Univ., Newcastle upon Tyne, United Kingdom, United Kingdom

Abstract: Many neurons in primary visual cortex (V1) of primate are selective for binocular disparity, and the standard model used to explain this is the binocular energy model (BEM). This asserts that inputs from each eye are summed linearly, then squared and combined into a single neural response. Such a model is in the form of an LNLN cascade (linear-nonlinear-linear-nonlinear), where the first nonlinearity is quadratic and the second is a spiking nonlinearity. While such a model offers a good first-order description of binocular computation of V1 neurons, it falls short in details, which has led to various other suggestions of how computations performed by V1 neurons deviate from the BEM prediction. Because LNLN cascade models can be fit to recordings of V1 directly, we used a range of mathematical forms to test the assumptions of the BEM and determine alternative models of different mathematical forms and fit their parameters. We recorded disparity-selective neurons in V1 of awake, fixating monkeys during

presentation of ternary bar stimuli with a range of disparities, presented using a haploscope. We then used maximum likelihood estimation to fit LNLN cascade models, in order to determine the form of nonlinearities and relationships between the filters in each eye that best describe V1 neurons. We found that models not constrained to quadratic nonlinearities better predict neural responses, including the ability to reproduce their disparity tuning. Furthermore, when nonlinearities were not quadratic, models tended to recombine spatiotemporal processing features with less symmetry between eyes and a greater range of spatial frequencies than the BEM. Such empirical results are consistent with theoretical predictions for disparity selectivity in the context of natural image processing, and furthermore might be leveraged to reveal a mechanistic understanding of how binocular processing is constructed in V1.

Disclosures: **F. Bartsch:** None. **S. Henriksen:** None. **B.G. Cumming:** None. **D.A. Butts:** None.

Poster

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MOST 103-2321-B-002-028

MOST 104-2320-B-002-065-MY3

Title: Spatial receptive fields of color-responsive neurons in macaque V1

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Abstract: Spatial receptive fields have been studied to understand the properties of color- and luminance-responsive neurons in primary visual cortex (V1). In macaque V1, many neurons responding to color are highly selective for orientation and spatial frequency (Johnson et al., 2001; Friedman et al., 2003). One might predict that the receptive field structures of color-responsive neurons would consist of multiple elongated sub-regions (like simple cells). However, previous studies had shown mixed results: some found simple-cell-like receptive fields by using dense noise (Horwitz et al., 2007; Johnson et al., 2008), whereas others found receptive fields that were blub-like and less elongated when using sparse noise (Conway and Livingstone, 2006). Here we measured spatial receptive fields of V1 color-responsive neurons with three

different stimulus ensembles: Hartley gratings, binary white noise, and binary sparse noise. All three stimulus ensembles consisted of equiluminance colors (red and green that represent different cone weights). Receptive fields were calculated by reverse correlation and fitted with the 2-D Gabor function. We studied a total of 226 V1 units and found that Hartley maps had significantly higher aspect ratios and greater numbers of subregions than white-noise and sparse-noise maps. There was a negative correlation between the circular variance measured with drifting gratings and the aspect ratio of the map (significant correlation was found in both Hartley and white noise, but not in sparse noise). Moreover, we found that double-opponent color cells had significantly higher aspect ratios that single-opponent color cells (double- and single-opponent were classified based on spatial frequency tuning, Johnson et al 2008). In summary, the receptive field of color-responsive neurons may change accordingly with different stimulus ensembles. For neurons that are well tuned for orientation, the tuning properties can be well predicted by their receptive field properties.

Disclosures: C. Yeh: None. **W. Huang:** None. **H. Wu:** None. **Y. Pei:** None.

Poster

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Topic: D.07. Vision

Support: Natural Science Foundation of China grant (31230030)

Title: V1 neurons respond to second order grating: Evidence from two-photon imaging

Authors: *S. GUAN[1], N. JU[2], Y. SHAO[2], C. YU[1,3,4], S. TANG[3,2], L. TAO[2]
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Abstract: Second order, contrast-defined stimulus information often plays an important role in middle level vision. Here we compare response properties of V1 neurons to first- and second-order gratings, via two-photon calcium (GCaMP5) imaging of awake, fixating macaque. The visual stimulus consists of first -order (luminance defined, at 90% contrast) and second-order (contrast-defined, at 0.0583 RMS contrast) Gabor gratings. The grating varied at 6 spatial frequencies (0.25-8 cpd) and 12 orientations (-45-120 deg) and was drifting at 2 cycles/sec. We recorded a total of 877 neurons (with orientation OSI > 0.5, ANOVA $p < 0.05$) at a single site (a window of 850x850 um at 3-deg parafovea). We found that 605 neurons (69%) respond only to first-order gratings, 121 (14%) respond only to second-order gratings, and 151 (17%) respond to both first- and second-order gratings. The median peak response frequency to first-order gratings was 2.3 cpd, while the median peak response frequency to second-order gratings was 1.04 cpd.

In particular, for neurons responding to both first- and second-order gratings, we observed a peak response frequency decrease from 2.3 cpd to 0.93 cpd (first- to second-order). Roughly half of these neurons had a peak response frequency shift greater than 1 octave. Furthermore, about half (46%) of these neurons had peak orientation shifts of less than 10 degrees, and 35% had peak orientation shifts larger than 30 degrees (and up to 90 degrees). The spatial frequency and orientation bandwidths (half-width at half maximum) remained the same on average. These results confirm the significant role V1 plays in second-order stimulus processing. The smaller number of second-order responsive neurons and their corresponding peak frequency shift to lower frequencies are consistent with the facts that human perception is less overall sensitive to second-order gratings, but relatively more sensitive at lower spatial frequencies.

Disclosures: **S. Guan:** None. **N. Ju:** None. **Y. Shao:** None. **C. Yu:** None. **S. Tang:** None. **L. Tao:** None.

Poster

057. Cortical Coding and Oscillations

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Program#/Poster#: 057.20/BB3

Topic: D.07. Vision

Support: NIH Grant EY018613

Title: Tuning of MT neurons depends on stimulus contrast in accord with canonical computation

Authors: *A. S. PAWAR[1], S. GEPSHTEIN[1], S. E. SAVEL'EV[2], T. D. ALBRIGHT[1]
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Abstract: Background: Sensory systems are highly selective, but different measures of selectivity are used in behavioral and physiological studies of selectivity: threshold assays in the former and suprathreshold assays in the latter. To understand neural mechanism of behavioral selectivity, it is important to compare behavioral and physiological characteristics of selectivity in similar terms. Here we address this challenge using physiological and computational methods. We study spatial frequency (SF) and temporal frequency (TF) tuning of cortical neurons at contrast threshold and above, and compare the results with predictions of a canonical model of cortical computation.
Methods: We measured responses of 140 neurons in the middle temporal (MT) area of the visual cortex of two alert macaque monkeys engaged in a fixation task. The stimuli were sinusoidal luminance gratings at multiple contrasts (0.005-1), five values of SF, and one to four values of TF. For each cell, we obtained response functions and contrast sensitivity functions (CSF). Response function was defined as the firing rate measured for multiple SF at a fixed

contrast, and CSF was defined as the reciprocal of the contrast at which the firing rate was one standard deviation above the resting rate. We compared the peak SF of response functions (peak response) to peak SF of CSF (peak sensitivity), and also studied how peak response changed across contrast and TF.
Results: In both monkeys, peak responses changed with contrast in most cases. The mean change was toward higher SF. The amount of change depended on TF: it was large at low TF but shrank with progressively higher TF. Peak sensitivity and peak response matched only in a narrow range of low contrasts, below 0.15, and only at high TFs. Using a canonical model of inhibition-stabilized cortical circuit (*arXiv*:1410.4237) we found that frequency tuning of the circuit generally depends on contrast, similar to MT neurons. Whether the tuning drifts to lower or higher SF depends on the balance of excitation and inhibition in the circuit. This result suggests that frequency tuning of cortical neurons is driven by properties of the local circuit and is not imposed by feedforward or other connectivity.
Conclusions: Tuning of MT neurons to spatial frequency changes with luminance contrast. The amount of change depends on stimulus temporal frequency. Only at high temporal frequencies do threshold and suprathreshold tuning match, and only in a narrow range of contrasts. This behavior is predicted by a model of canonical cortical computation, challenging the standard conception of receptive field properties of MT neurons.

Disclosures: A.S. Pawar: None. **S. Gepshtein:** None. **S.E. Savel'ev:** None. **T.D. Albright:** None.

Poster

057. Cortical Coding and Oscillations

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Topic: D.07. Vision

Support: FLAG-ERA JTC 2015 project CANON

Title: Orientation-selective population responses in ferret visual cortex

Authors: *L. M. F. KLAVER, A. G. WILLIAMS, L. CASADO-ROMÁN, T. SIKKENS, L. VAN MOURIK-DONGA, C. M. A. PENNARTZ, C. A. BOSMAN
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Abstract: Neurons in V1 are known to respond to multiple visual features including location in space (i.e. receptive fields), direction, and orientation. It is also known that visual properties such as receptive fields can be inferred from electrophysiological population responses such as event-related potentials or from high-frequency gamma oscillatory responses. Both cellular and population responses to visual features can be modulated by other sensory modalities as well. It

has previously been shown that orientation-selective neurons in mouse visual cortex can change their tuning when a sound is added to accompany a visual stimulus, however how such modulatory effects are manifested in ferret visual cortex is currently unknown.
The visual cortex of the domestic ferret differs from that of rodents in that it contains direction and orientation selective cells which are organized into orientation columns. This makes the ferret an excellent model to study visual features and how they can be modulated by sound.
In this study, we aimed to find whether it is possible to deduce the orientation of a visual stimulus from a population response (such as the local field potential (LFP)) and how this response is supported by cortical organization. Moreover, we asked whether these population responses are modulated by the presence of sound.
We performed awake, chronic, head-fixed electrophysiological recordings from ferret primary visual cortex (area 17) using silicon probes. The animals passively viewed drifting full-field gratings of different orientations, in the presence or absence of sound.
Consistent with previous studies in anesthetized cats, preliminary results show that orientation tuning is reflected by increases in gamma activity (30-60 Hz). However in addition, we also find corresponding increases in beta-power (ß,12-30 Hz). This ß orientation selectivity is mostly compartmentalized to deeper layers. Moreover, these ß-LFP responses do not necessarily correspond with the orientation tuning of single unit responses measured from that population of neurons. As expected, we find both fast- and regular-spiking orientation selective cells, but only a subset of these neurons phase-lock to the ß frequency for its preferred orientation. Finally, ß orientation tuning was modulated by sound. These results indicate that ß oscillations in area 17 can convey information about orientation, and shape temporal patterning of orientation-selective neurons. The current findings suggest that alignment of cortical spikes to beta phase facilitates early sensory processing.

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Poster

057. Cortical Coding and Oscillations

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Topic: D.07. Vision

Title: Cortical magnification factors within 0.5 degree eccentricity in rhesus monkeys

Authors: *A. G. XU, A. ZHAO, A. W. ROE
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Abstract: Previous studies on cortical magnification factors (CMF) in non-human primates and humans indicate that more cortical areas are deployed in processing central than peripheral visual

field. However, there is still no good coverage of data within 1 degree eccentricity of visual field. In this study, we presented arc stimuli at eccentricity 0.01, 0.1, 0.2, 0.3, 0.4 and 0.5 degree to anesthetized rhesus monkeys, and recorded optical intrinsic signal changes in visual cortex V1. We then identified cortical areas correspond to each stimulus and estimated CMF. We found that CMF decreases with increasing eccentricity even within 0.5 degree eccentricity. This general trend is consistent with previous findings outside of foveal vision. However, we also found that V1 areas for separated foveal stimuli are largely overlapped. This suggests that cortical organization for foveal visual field is probably very different from that for visual field outside of fovea.

Disclosures: A.G. Xu: None. **A. Zhao:** None. **A.W. Roe:** None.

Poster

057. Cortical Coding and Oscillations

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FAPESP Research, Innovation and Dissemination Center for Neuromathemat- ics (grant no. 2013/07699-0, S. Paulo Research Foundation)

Title: Gamma oscillations in the retinogeniculate system of the cat do not play a role in natural vision

Authors: *S. NEUENSCHWANDER[1], G. ROSSO[1], F. FREITAG[1], J.-B. DE SAINT AUBERT[2], E. J. TEHOVNIK[1], K. E. SCHMIDT[1], J. BARON[3]
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Abstract: Gamma oscillations in the retina are transmitted to the lateral geniculate nucleus (LGN) and to the cortex, and are thought to encode stimulus size and continuity. Support for these conjectures were obtained mostly in the anesthetized cat, and visual stimuli were often limited to whole-field flashes. Here, we aim filling this gap by characterizing the oscillatory behavior of responses in the awake cat, under naturalistic conditions, such as during free-viewing of a visual scene. Simultaneous multiple-electrode recordings were made from the LGN and the retina of anesthetized cats (N= 5) and from the LGN of awake cats (N= 2). Comparisons were made for responses to natural movies and flashed stationary light stimuli, during anesthesia by halothane (or isoflurane) and by ketamine (control experiments). To test specifically the role of retinal oscillations in encoding stimulus size we designed a protocol made of a light circle of

varying size along the trial. Spike sorting techniques allowed us to study separately the ON- and OFF- components of the responses. Analysis consisted in measuring coherence for single cell spiking activity as a function of time. In the anesthetized cat, retinal oscillations were found to be surprisingly dependent on halothane (and isoflurane) concentration levels. In the absence of halothane (ketamine controls) or in the awake cat, oscillations were missing. These findings suggest that gamma synchronization in the retina is artifactual and consequently irrelevant for natural vision.

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Poster

057. Cortical Coding and Oscillations

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FAPESP Research, Innovation and Dissemination Center for Neuromathemat- ics (grant no. 2013/07699-0, S. Paulo Research Foundation)

Title: Do grating stimuli bias our concepts on cortical gamma coherence? A study in capuchin monkey V1

Authors: S. NEUENSCHWANDER[1], K.-S. ROCHA[1], L. DANTAS[1], R. FAUSTINO[1], *K. E. SCHMIDT[1], J. BARON[2]
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Abstract: Cortical gamma oscillations have been implicated in perceptual binding and visual attention. So far, most evidence in support of this hypothesis are based on studies that used artificial, simplified stimuli, such as moving gratings and bars. Recently, a more naturalistic approach led to diverging conclusions. In human subjects required to hold fixation, ECoG responses showed gamma for gratings but not for static images and pink noise (Hermes et al., Cereb Cortex 25, 2951-2959, 2015). In capuchin monkey V1, spiking activity exhibited strong beta but no gamma during free viewing of static images (Ito et al., Cereb Cortex 21, 2482-2497, 2011). Contrary to these findings, analysis of ECoG signals in the early visual cortex of macaque monkeys revealed strong gamma components for natural scenes (Brunet et al., Cereb Cortex 25, 918-926, 2015). Here, we aim at clarifying these discrepancies using an experimental paradigm that allows direct comparisons between fixation vs. free viewing conditions and artificial vs.

natural stimulation regimes. Within a trial, monkeys were required to fixate for 2 s, after which they could freely inspect the visual stimulus for another 2 to 4 s. In some recording sessions, monkeys were also exposed to real world scenes, such as viewing of other monkeys, humans or real objects. This last condition, albeit not as well controlled, provided a means of assessing visual responses in truly naturalistic conditions. Recordings were made using 2-4 quartz-insulated electrodes placed at the central and peripheral representation of V1. Our results show that gratings at preferred orientations are capable of inducing strong gamma responses (from 40 to 90 Hz) during both fixation and free-viewing conditions (N= 3 monkeys). In contrast, gamma is nearly absent while freely viewing natural images and movies on a monitor screen. Similar negative results were obtained for real-world scenes. Notwithstanding, the same eccentricity-dependent effect on oscillation frequency described previously for the macaque (Lima et al., Cereb Cortex 20, 1556-1573, 2010) was also evident in our data. This new finding in a new-world monkey reinforces our hypothesis that the functional architecture imposes important constraints on coherence dynamics in the cortex. Overall, the present study weakens the notion that gamma is necessary for visual processing in natural conditions.

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Poster

057. Cortical Coding and Oscillations

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Support: NIH R00MH099654

Title: Stimulus-locked gamma oscillations in V1 carry learned spatiotemporal information

Authors: E. A. DE LAITTRE[1], R. W. SCHECTER[1], B. H. PRICE[1], *J. P. GAVORNIK[2]
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Abstract: The ability to recognize and predict temporal sequences is a key feature of cognition and sensory processing across modalities, but little is known about the underlying mechanisms involved. Recent evidence suggests that learned sequence recognition and prediction can occur as early in the visual processing hierarchy as primary visual cortex (V1) . Repeated exposure over days to the same sequence of visual stimuli causes potentiation of visually evoked responses in mouse V1 that is specific for the timing and order of the trained stimulus sequence (Gavornik & Bear, 2014). The specificity of the learned response has been characterized by potentiation of evoked potentials seen in the low frequency component (<60Hz) of the local field potential in V1, and by concurrent changes in spiking activity. Here we report that repeated exposure to

sequence stimuli also causes changes to evoked LFP responses in the high gamma range (60-100Hz), which are likewise specific to the order and timing of the stimulus sequence. We show that this effect is blocked by local infusion of scopolamine, a muscarinic acetylcholine receptor antagonist shown to block potentiation of low frequency VEPs in sequence learning. The implications of these findings are unclear given the many sources and roles implicated for both acetylcholine and gamma rhythms in cortex and specifically V1. Further exploration of the relationship between low frequency VEP potentiation and neuronal synchrony in sequence learning and recognition is needed to interpret these results.

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Poster

057. Cortical Coding and Oscillations

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Topic: B.09. Physiological Properties of Neurons

Support: NIMH 1P50MH094271

Title: Enhanced gamma oscillations drive perineuronal net instability and cortical plasticity

Authors: *H. H. LEE[1], A. E. TAKESIAN[1], Z. YE[2], N. W. HODGSON[1], T. K. HENSCH[2]
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Abstract: Cortical gamma oscillations (30-80Hz) are generated by local or long-range fast-spiking, parvalbumin (PV)-expressing inhibitory neurons. Yet, the critical components within these GABA circuits that regulate gamma oscillations remain elusive. Here, we confirm an enrichment of the alpha1 subunit of GABA(A) receptors in mature cortical PV+ cells. Cell-selective removal of this subunit (PV-alpha1 KO mice) disrupts their reciprocal inhibition, while keeping excitatory input intact. Strikingly, this excitatory-inhibitory (E-I) imbalance upon PV+ cells alone results in a globally enhanced baseline gamma power across brain regions in freely behaving PV-alpha1 KO mice. Enhanced gamma power was accompanied by oxidative stress preferentially in PV+ cells, as revealed by a variety of markers. First, the mitochondrial DNA damage marker, 8-oxo-dG, was intensified in PV+ cells. Second, cystathionine accumulation in cortical homogenates confirmed activation of the reverse trans-sulfuration pathway to produce the primary cellular antioxidant, glutathione, essential for maintaining neuronal redox state and mitigating oxidative stress. Third, the ratio of reduced:oxidized glutathione (GSH:GSSG) was decreased. Fourth, active microglia were increased in close proximity to PV+ cells, suggesting enhanced structural modulation. Finally, this was supported by a persistent turnover and weakening of the tight extracellular matrix perineuronal net (PNN), which enwraps PV+ cells to

buffer reactive oxygen species and serves as a structural brake on plasticity. Consequently, cortical critical periods remained open into adulthood across multiple brain regions, such as the loss of visual acuity in primary visual cortex (V1) following monocular deprivation or the acquisition of acoustic preference in medial prefrontal cortex (mPFC). All phenotypes of the PV-alpha1 KO mice could be restored to wildtype levels by specifically suppressing presynaptic excitatory input to PV+ cells with a group II metabotropic glutamate receptor agonist. Importantly, these receptors are not found in PV+ cells or basal forebrain per se, indicating the E-I balance upon cortical PV+ cells is pivotal. Together, our results reveal a role for gamma oscillations to drive cortical plasticity throughout life by heightened PV+ cell metabolic demand, oxidative stress and subsequent PNN weakening. The PV-alpha1 KO mice might also recapitulate cellular and circuit defects of at-risk subjects exhibiting widespread elevated baseline gamma power prior to first psychotic episode, thereby offering a testbed for novel prophylaxis strategies.

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Poster

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Topic: G.07. Other Psychiatric Disorders

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Title: Gamma oscillations of sensory cortex in genetic and pharmacological models of schizophrenia

Authors: *C. G. WELLE[1], D. CONTRERAS[2]
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Abstract: Human patients with neuropsychiatric disorders such as schizophrenia have altered patterns of gamma frequency activity. Changes in gamma oscillations occur not just in the higher cognitive areas that have long been associated with the disease state, but also in basic sensory processing areas such as primary visual and auditory cortex.
Here, we characterized the alterations in gamma activity in the primary visual cortex of mice with endophenotypes of schizophrenia. We used two well established manipulations, namely,

subanesthetic injections of ketamine (30 mg/kg, i.p.) and the neuregulin-1 (NRG1+/-) knockout mouse, that have been shown to produce behavioral and physiological endophenotypes of schizophrenia in the mouse. We recorded local field potentials (LFPs) with a multisite probe (Neuronexus) inserted perpendicular to the cortical surface, or single units using individually moveable tetrodes (Thomas Recording). For acute recordings of LFPs and single units, mice were anesthetized with a mix of isoflurane and xylazine in order to obtain a stable low amplitude spontaneous baseline pattern recorded in the LFPs and robust evoked visual responses. For chronic, non-anesthetized recordings of LFP, a multisite probe was implanted normal to the cortical surface and allowed to stabilize for one week before recording. Contrast modulated, full field drifting gratings were presented to anesthetized animals, while awake animals were exposed to a bright LED stimulus.
We show that pharmacological and genetic manipulations of the glutamatergic system alter the power of gamma oscillations (measured as the ratio of the area under the curve of 20-50Hz between visual response and baseline) in the mouse primary visual cortex in vivo. Both the administration of the NMDA receptor antagonist, ketamine, and the knockout of *neuregulin-1* produce an increase in the ongoing baseline gamma power. As a result, the signal-to-noise ratio of gamma activity induced by a sensory stimulus is decreased. In addition, entrainment of neurons in the superficial and deep layers to gamma oscillations in the LFP was reduced and orientation selectivity was diminished. Our results suggest that alterations in gamma oscillations found in patients with neuropsychiatric disorders may results from perturbed glutamatergic function, and may contribute to aberrant sensory perception.

Disclosures: **C.G. Welle:** None. **D. Contreras:** None.

Poster

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Title: Delta oscillations in schizophrenia: Insights from biophysically detailed modeling of networks of layer V pyramidal cells

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Abstract: Delta oscillations (0.5-4 Hz) are widely distributed brain oscillations observable with electroencephalogram (EEG) measurements most prominently during deep sleep, but also in association with mental tasks. During the awake state, their amplitude is known to be higher in schizophrenia (SCZ) patients than in healthy controls (Sponheim et al. 1994, *Psychophysiology*, 31:37-43), but the mechanisms for this amplification remain unknown. The delta oscillations seem to contain two components, one originating from the thalamus and the other from the neocortex (Neske 2015, *Front Neural Circ* 9:88). The thalamically generated delta oscillation stems solely from the intrinsic properties of the thalamocortical neurons, while the cortically generated delta oscillations are likely to rely on the intrinsic properties of layer V pyramidal cells (L5PCs). Moreover, as L5PCs integrate large numbers of inputs from thalamic nuclei, alterations in L5PC activity could crucially affect both components of the delta oscillation. Altered L5PC activity has also been suggested as a principal mechanism behind faulty perceptions, such as hallucinations, in mental disease (Larkum 2013, *Trends Neurosci* 36.3:141-51). Consistent with this hypothesis, a recent genome-wide association study of SCZ highlighted a large set of ion-channel and Ca^{2+}-transporter-encoding genes (Ripke et al. 2014, *Nature* 511(7150):421-7), many of which are expressed in L5PCs.
In this work, we study the contributions of the intrinsic L5PC properties to the generation and maintenance of delta oscillations using biophysically detailed modeling. We employ a reduced-morphology version (Mäki-Marttunen et al. 2016, *BMC Neuroscience*, 17(Suppl 1):P165) of a model of coupled L5PCs (Hay and Segev 2015, *Cereb cortex* 25.10:3561-71), which includes description of multiple Hodgkin-Huxley-type ion channels and intracellular Ca^{2+} dynamics. We modify the model parameters to mimic the small effects that are expected to be observed in common variants associated with SCZ (Mäki-Marttunen et al. 2016, *Biol Psych: Cogn Neurosci Neuroim* 1, 49-59). We show that the L5PC network gain and the responses of the network to delta oscillations are altered by variants of SCZ-associated ion-channel and Ca^{2+}-transporter-encoding genes. We also explore the effects of differential gene expression by varying conductances of the ion-channel species that correspond to genes whose expression in blood sample data of SCZ patients deviated from that of healthy controls. Our results contribute to the understanding of the altered delta power in SCZ patients and could ultimately lead to development of novel future treatments of the disorder.

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Poster

058. Visual Cognition: Decision Making

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Program#/Poster#: 058.01/BB12

Topic: D.07. Vision

Support: Muhlenberg College startup funding to PEW

Title: Testing fly visual behavior with a true 2-alternative forced-choice task

Authors: M. LOUKA, A. R. GRASSI, E. J. BEEBE, *P. E. WILLIAMS
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Abstract: Flies are attractive subjects for testing visual behavior because they are highly visual animals but have fewer visual brain areas than humans. This makes them potentially more tractable for dissecting the neural correlates of visual behavior. As Benzer (1967) showed with his countercurrent method, they are also easy to screen in large quantities for particular behaviors. Alternatively, flies can be tested rapidly on multiple trials by using mazes that are designed to create a 2AFC-like task. However, standard psychophysical protocols can be challenging to use in high-throughput experiments with flies, particularly when examining cognitively-oriented behaviors such as visual attention. In particular, flies are usually surrounded by other flies and view the same stimulus throughout multiple trials. This violates the expectations that subjects encounter randomly-selected stimuli at each choice point and make choices that are free from bias created by non-stimulus distractors. As Benzer noted, there are tradeoffs in the countercurrent and maze methods when attempting to ensure independent choices.
We custom designed and printed mazes for *Musca domestica* to identify features that would help optimize independent choice behavior in a high-throughput protocol. We found that: (1) Gauging independence by checking only to see that fly choices were binomially distributed was insufficient to uncover flaws that affect measures such as choice persistence. (2) Wall-following and line-of-sight behaviors were common but possible to minimize. (3) Stimuli could be randomly selected for each fly at each choice point while still maintaining relatively high throughput by using low-cost infrared sensors to track flies' movement through the apparatus in real time. We provide our protocols and STL design files freely for use or modification.

Disclosures: **M. Louka:** None. **A.R. Grassi:** None. **E.J. Beebe:** None. **P.E. Williams:** None.

Poster

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Support: Wellcome Trust 095668

Wellcome Trust 095669

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Title: Diverse responses of neurons in mouse superficial superior colliculus during a visual decision task

Authors: *S. SCHRÖDER, M. ALLEMAN, K. D. HARRIS, M. CARANDINI
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Abstract: Neurons in the superficial layer of the superior colliculus (sSC) receive input from retina and visual cortex and are thus thought to be mainly visual. We have shown, however, that their activity is modulated not only by visual stimuli but also by the animal's arousal as reflected by pupil size (Schröder et al., SfN, 2016). Here we ask whether sSC neurons might also deliver motor or task-related signals.

We trained mice to perform a 2-alternative unforced-choice visual detection task (Burgess et al., bioRxiv, 2016) and we imaged the activity of neuronal populations in sSC using two-photon microscopy. We used viral injection to express GCaMP6f in sSC neurons, and exposed posterior sSC using an implant that leaves cortex intact. During the task, a sinusoidal grating appeared in the left or the right visual field, and the mouse moved this grating towards the center of its visual field by turning a steering wheel with its forepaws. After stimulus onset, the mouse waited for an auditory cue before turning the wheel. If the wheel was turned in the correct direction within a fixed time limit, the mouse was rewarded with a drop of water; otherwise, a white noise sound was played. In some trials, no stimulus was presented and the mouse was rewarded for holding the wheel still. Pupil dilation was recorded as a measure of arousal.

We analyzed data obtained from two mice. The activity of many sSC neurons correlated with pupil diameter, as when the mouse was passively viewing visual grating stimuli. To study task-related responses, we adopted a general linear model to estimate response kernels for each task event, e.g. one kernel for left stimuli, one for right stimuli, one for the auditory cue, and so on. In contrast to using simple event triggered averages, this method distinguishes between responses to different events even when they are overlapping in time. In agreement with the visual role of

sSC, the recovered kernels show that many sSC neurons responded when the visual stimulus appeared in their receptive fields. But other neurons responded to other task events, such as the movement of the wheel, the water reward, the auditory cue, or the white noise sound. A small subset of neurons responded to multiple task events.
These results indicate that sSC in the mouse represents not only visual input and a generic measure of arousal, but also specific inputs of other sensory modalities, motor output, and reward-related signals. These representations expose functional differences among sSC neurons, which may perhaps correlate with differences in morphology, genetic makeup, or projection targets.

Disclosures: S. Schröder: None. **M. Alleman:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

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Topic: D.07. Vision

Support: Wellcome Trust 095668 and 095669

JSPS to DS

Title: Effects of bilateral spontaneous activity on mouse visual cortex during a visual detection task

Authors: *D. SHIMAOKA, K. D. HARRIS, M. CARANDINI
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Abstract: The responses of visual cortex to an identical visual stimulus fluctuate prominently across trials. This neuronal variability is due to spontaneous activity shared by large populations of neurons (e.g. Scholvinck et al. 2015) and has been suggested to cause fluctuations in visual perception (e.g. Ress & Heeger 2003). At a large-scale, spontaneous activity is often observed as symmetrical waves shared by both hemispheres (Mohajerani et al., 2013). To what extent does this bilateral spontaneous activity account for variability in visual responses?
To address this question, we measured mean membrane potential activity using wide-field imaging from both hemispheres while mice engaged in a visual detection task. We expressed a genetically-encoded voltage indicator VSFP-B1.2 in all layers of excitatory neurons using an intersectional transgenic approach (Madisen et al., 2015). For each mouse, the locations of V1 and other visual areas were identified from visual field sign map (Sereno et al., 1994). The mice were then repeatedly imaged (12 sessions from each of 2 mice) during a 2-alternative visual

detection task, in which mice turn a steering wheel to report whether a grating was presented on the left or right monocular visual field (Burgess et al., 2016).
To determine how membrane potential responses to stimuli were related to bilateral spontaneous activity, we first predicted the response of the each V1 hemisphere from the other, using a linear regression analysis trained on spontaneous activity. Subtracting this prediction during stimulus responses had no significant effect on mean response amplitude ($p=0.8$), but reduced trial-to-trial variability by more than 4.9±1.3%, a significant effect ($p=0.0076$, paired t-test, $n=4$ hemispheres). By comparison, if instead of subtracting the signals from contralateral visual cortex we subtracted the signals from ipsilateral frontal cortex, the responses in V1 became 0.5±0.3% less variable ($p=0.03$).
These results indicate that that the large bilateral spontaneous fluctuations seen in mouse V1 provide a marked contribution to variability in visually-evoked activity in V1.

Disclosures: D. Shimaoka: None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

058. Visual Cognition: Decision Making

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Topic: D.07. Vision

Support: Wellcome Trust 095668 and 095669

Sir Henry Wellcome Fellowship 106101

Title: Mouse frontal cortex combines perceptual signals and recent outcomes to compute the expected return of actions

Authors: *A. LAK, M. OKUN, A. B. SALEEM, C. HASTINGS, N. A. STEINMETZ, P. ZATKA-HAAS, K. D. HARRIS, M. CARANDINI
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Abstract: Making decisions under uncertainty requires estimating the expected return of actions. When the sensory environment is uncertain and action outcomes fluctuate over time, the expected return depends on both immediate perception and recent outcomes. To find neuronal correlates of this computation, we recorded from large populations of neurons in medial prefrontal cortex (mPFC), while mice performed a choice task under perceptual and outcome uncertainty.
We expressed Channelrhodopsin-2 in midbrain dopamine (DA) neurons of DAT-Cre mice, implanted an optical fiber above the ventral tegmental area and trained them in a two-alternative forced choice visual task (Burgess et al, *bioRxiv*, 2016). In each trial, a grating appeared to the

left or the right of the monitor, and the mouse turned a steering wheel to indicate the grating's position. We varied stimulus contrast across trials and obtained high-quality psychometric curves. To manipulate choice outcomes, in alternating blocks of trials, we paired correct choices towards one of the two stimuli with brief optogenetic DA stimulation, in addition to the normal water reward. The psychometric curves shifted towards the side paired with DA stimulation, indicating that mice integrate immediate sensory and past DA reinforcement signals when making decisions. A reinforcement learning (RL) model incorporating perceptual uncertainty and past outcomes into the choice computation (Lak et al, Current Biology, 2017) could account for trial-by-trial choices.
While mice performed the task, mPFC neurons exhibited heterogeneous activity, responding to one or a few task events, such as the trial onset beep, visual stimulus, action onset, or outcome. We quantified these responses by modeling each neuron's firing rate as a sum of temporal kernels aligned to each task event. For the majority of neurons, the responses observed between the stimulus and action onset could be accounted for by actions. These pre-action responses scaled with the contrast of the visual stimulus, but were almost independent of choice direction (left/right). Moreover, responses varied between blocks, reflecting the upcoming choice outcome (nothing, water, or water + DA stimulation). Finally, correlation of pre-action activity and the value estimates from the RL model showed that ~25% of task-responsive neurons encode the expected return of actions on a trial-by-trial basis.
These results suggest that a subset of mPFC neurons reflect the expected return of actions under perceptual and outcome uncertainty. These signals emerge prior to action onset and could inform downstream structures about the value of ongoing choices.

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Poster

058. Visual Cognition: Decision Making

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Topic: D.07. Vision

Support: CoMPLEX Studentship

Wellcome Trust 095668

Wellcome Trust 095669

Title: Mapping perceptual decisions to cortical regions

Authors: *P. ZATKA-HAAS, N. A. STEINMETZ, M. CARANDINI, K. D. HARRIS
Univ. Col. London, London, United Kingdom

Abstract: Perceptual decisions involve a complex interaction of several brain areas. The neocortex is thought to play a major role in this process. However, it is difficult to establish which cortical areas are causally relevant, and what their individual roles are. Here we show that a combination of optogenetic inactivation and choice modeling can identify precise contributions of specific cortical areas in a perceptual decision task.
We trained mice in a two-alternative unforced visual discrimination task (Burgess et al, bioRxiv 2016). Mice were rewarded for turning a wheel left or right to indicate which hemifield contained a grating stimulus of higher contrast, and for refraining from turning the wheel (a "no-go" choice) if no stimulus was present. Mice were bred to express Channelrhodopsin-2 in Pvalb-expressing inhibitory neurons, and implanted with a transparent skull cap. On a random subset of trials, a 473 nm laser locally inactivated one of 52 cortical sites.
Inactivation of visual and secondary motor areas (VIS and M2) increased the fraction of choices made towards the side of inactivation, and decreased choices made towards the contralateral side. These behavioral perturbations depended on the stimulus contrast. Inactivation of all other areas decreased no-go choices, lowering overall performance.
To capture these effects, we employed a logistic choice model. The model fits the probabilities of choosing left, right, or no-go using parameters reflecting choice bias, stimulus sensitivity, and a nonlinear function of contrast parametrized by the half-maximal contrast c50. Inactivation of either VIS or M2 induced a bias away from choices made towards the contralateral side of inactivation. Inactivation of VIS also increased c50 for visual stimuli on the contralateral side. Inactivation decreased sensitivity for all inactivated regions nonspecifically. These results suggest that visual areas are needed both for the functional effect of stimulus contrast on behavior, and for action selection, whereas M2 is needed only for action selection.
To further explore the role of these areas, we performed widefield imaging and electrophysiological recordings in mice performing a similar task. We extended the behavioral model to incorporate regressors for the neural activity. With cross-validation, we quantified whether neural activity offers improved prediction of choice beyond that contained in the stimulus. Preliminary results reveal widespread decoding of choice at the time of the motor response. These findings prepare us to investigate these areas in greater detail, to further uncover the causal neural structures which drive visual discrimination.

Disclosures: P. Zatka-Haas: None. **N.A. Steinmetz:** None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

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Topic: D.07. Vision

Support: Wellcome Trust 095668

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Human Frontier Sciences Program Postdoctoral Fellowship

Marie Curie Postdoctoral Fellowship

Title: Neuronal populations supporting vision, action, and reward across the mouse brain

Authors: *N. A. STEINMETZ, M. CARANDINI, K. D. HARRIS
Univ. Col. London, London, United Kingdom

Abstract: Behavior arises from neuronal activity patterns, but whether the relevant activity is private to a small number of brain regions, as typically studied, or instead distributed and coordinated widely across many regions, remains unknown. Measuring the activity of distributed populations, at single neuron spatial resolution and millisecond temporal resolution, is therefore critical to understanding how behaviors are generated.
We trained mice to perform a visually-guided perceptual decision task, involving visual, auditory, motor, decision-, and reward-related components (Burgess et al., bioRxiv 2016). In this task, mice were trained to give one of three responses (choose left, choose right, or choose neither) depending on the relative contrast of two simultaneously presented visual stimuli, with an auditory go cue. We recorded the activity of thousands of neurons during task performance using acutely-inserted Neuropixels electrode arrays (www.ucl.ac.uk/neuropixels), whose output was processed via kilosort (Pachitariu et al, bioRxiv 2016). The arrays span ~4 mm of tissue and thus record simultaneously across diverse brain regions. By reconstructing electrode locations based on fluorescent dye labeling, we established that the recorded neurons were located in >40 brain regions, including: sensory, parietal, frontal, and motor isocortex; multiple thalamic nuclei; hippocampus; the superior and inferior colliculi; the striatum; and multiple midbrain structures. To understand how this distributed neuronal activity related to multiple aspects of task performance, we fit the activity of each neuron as a sum of temporal kernels triggered on each of the task components (visual stimulus onset, auditory go cue, response execution, reward delivery, and others). We detected prominent visual responses in visual cortex, frontal cortex, and striatum. However, representations of motor response execution and reward were distributed especially broadly, and were observed in nearly every region we recorded (for example sensory and motor cortex, superior colliculus, and multiple thalamic regions). These highly distributed representations suggest that information pertaining to actions and rewards pervade essentially the entire brain.

Disclosures: N.A. Steinmetz: None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

058. Visual Cognition: Decision Making

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Title: Information flow across long-range cortical and subcortical circuits coordinates sensorimotor behavior

Authors: *R. HUDA, G. N. PHO, L. GUNTER, G. SIPE, M. SUR
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Abstract: Converting sensory inputs to goal-oriented motor actions is a fundamental task of the nervous system. While previous studies have shown that even simple sensorimotor behaviors require coordinated activity across a diverse array of brain regions, how flow of information between areas contributes to specific aspects of decision-making remains unclear. Consistent with anatomical criteria of a sensorimotor area, we found that the anterior cingulate cortex subdivision of the prefrontal cortex (PFC) receives strong sensory inputs from the visual cortex (VC) and sends outputs to the motor layer of the superior colliculus (SC), suggesting that it bridges sensation with action. To test this hypothesis, we developed a two-alternative forced choice task in which head-fixed mice report the spatial location of a visual stimulus by rotating a ball. We found that optogenetic inactivation of VC, PFC, or SC compromised performance on the task. Importantly, projection-specific optogenetic experiments revealed that VC inputs to PFC and PFC inputs to SC are necessary, suggesting that information flow across these long-range circuits plays a critical role during task performance. Next, we used two-photon imaging to record the activity of PFC neurons during the task. Decoding analysis revealed that PFC neurons encode information about the location of the sensory stimulus and the choices made by the animals, suggesting that PFC neurons participate in the sensorimotor transformation process. We are currently performing recordings from PFC neurons that project to the SC to determine if they encode specific aspects of the task. Together, our experiments suggest that visual information flows from VC to PFC, where it is converted into a motor plan and subsequently routed to the SC for motor execution, highlighting how communication across cortical and subcortical circuits contributes to sensorimotor behaviors.

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Poster

058. Visual Cognition: Decision Making

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Title: Probing V1 responses in freely moving rats performing a visual discrimination task

Authors: *A. ZHANG[1,2], A. M. ZADOR[2]
[1]Watson Sch. of Biol. Sci., Cold Spring Harbor, NY; [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: The pathways necessary for animals to perform perceptual decision-making tasks are often modality- or task-specific. Here we set out to test the hypothesis that tasks involving different stimulus modalities but the same motor report and task structure recruit similar sensory processing mechanisms. We have previously established the role of auditory corticostriatal projection neurons in driving learning and performance of an auditory frequency discrimination task ("cloud of tones" task) in rats (Znamenskiy and Zador 2013, Xiong et al 2015). We have now designed a directly analogous visual discrimination task for freely moving rats, in which spatial location replaces auditory frequency as the task-relevant variable. In this task, subjects are presented with a set of distributed flickering dots (a "cloud of dots"), and are asked to judge whether there are more dots in the upper or lower visual hemifield. As in the cloud of tones task, subjects report their choice with a nosepoke into the corresponding water delivery port. Subjects readily learn to perform this task at high levels of accuracy. We are currently using tetrodes to characterize responses of neurons in visual cortex of animals performing this task. We compare V1 activity elicited by the cloud of dots stimulus to responses to standard visual stimuli, such as drifting gratings, and ask how our stimulus is processed within or independent of the context of the task. Furthermore, we ask how the task-related variables encoded in V1 compare to those encoded in our auditory recording dataset.

Disclosures: **A. Zhang:** None. **A.M. Zador:** None.

Poster

058. Visual Cognition: Decision Making

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Topic: D.07. Vision

Support: ERC starting grant NEUROOPTOGEN

Title: Layer dependence of decision-related activity in the macaque visual cortex

Authors: *H. NIENBORG, K. QUINN, L. SEILLIER, S. CLERY, P. POURRIAHI
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Abstract: During perceptual decisions the activity of task relevant sensory neurons typically carries information about an animal's perceptual choice as well as the sensory stimulus ("choice correlations"). The implications of choice correlations for the link of the sensory neurons to perception have received substantial attention. Typically, they have been compared across sensory areas or tasks, while the within area processing has often been ignored.
Here, we examined the laminar profile of choice correlations within macaque visual areas V2 and V3. We recorded the extracellular spiking activity using multichannel linear arrays spanning V2 or V3, respectively, while macaque monkeys performed a disparity discrimination task similar to that reported previously (Nienborg and Cumming, 2009). We identified the input layers using current-source density analysis to align the laminar positions across sessions. We found that in V2 choice correlations were most pronounced in the deep layers (n=182), whose input is thought to be dominated by feedback. After the initial increase in choice-correlations after stimulus onset, this laminar profile changed little throughout the trial. Moreover, the neuronal ability to discriminate the stimuli (d') was most pronounced in the input layers, i.e. the laminar profile of d' could not account for that of choice correlations. Our preliminary results from area V3 suggest a different laminar profile and roughly similar choice correlations across layers (n=47), which may reflect the fact that decision-related signals are inherited from V2.
We also used a behaviorally validated metric based on pupil size (Kawaguchi et al. 2017) to infer the animal's decision confidence. Behaviorally, the animals relied more strongly on the stimulus on high than low confidence trials, throughout most of the trial. Late in the trial, however, they weighted the stimulus somewhat more strongly on low confidence trials. As expected, choice correlations had a tendency to be higher for high-confidence than low-confidence trials. However, contrasting with the behavior this effect was most pronounced late in the trial.
Together, these preliminary analyses are consistent with a decision-related feedback signal, predominantly to the deep layers, that is stronger when the animal's decision confidence is higher, and inherited downstream.

Disclosures: **H. Nienborg:** None. **K. Quinn:** None. **L. Seillier:** None. **S. Clery:** None. **P. Pourriahi:** None.

Poster

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Support: ERC starting grant NEUROOPTOGEN

Title: Evaluating perceptual strategy using decision confidence inferred from pupil size in macaques

Authors: *K. KAWAGUCHI[1], S. CLERY[1], P. POURRIAHI[1], L. SEILLIER[1], R. M. HAEFNER[2], H. NIENBORG[1]
[1]Ctr. For Integrative Neurosci., Tübingen, Germany; [2]Brain & Cognitive Sci., Univ. of Rochester, Rochester, NY

Abstract: Decision confidence is a useful parameter in the study of perceptual decision-making. Measuring decision confidence in animals typically increases the complexity of the behavioral task, and hence requires additional training. Here, we explored pupil-size measurements to infer decision confidence in two macaque monkeys (202 and 80 sessions for animal 1 and 2, respectively) performing a disparity discrimination task (cf. Nienborg and Cumming, 2009). The contrast and mean luminance of the stimuli were constant across trials allowing us to isolate pupil size modulation under constant illumination. Consistent with arousal-linked modulation in pupil size we observed a decrease in pupil size throughout a session, presumably resulting from satiation. When removing these slow trends throughout a session, we found that predictable changes in the available reward size were reflected in trial-by-trial fluctuations in pupil size suggesting they reflected the animals' motivation ($p<10^{-32}$, $p<10^{-18}$ across sessions for monkey 1 and 2, respectively). In addition, we observed that pupil size towards the end of the stimulus presentation was larger in easy (high stimulus strength) trials than hard (low stimulus strength) trials. We wondered whether this modulation reflected the animals' decision confidence driven by reward expectation and the learned probability of making a correct choice. To quantify this modulation we averaged the pupil size over 250ms prior to the stimulus offset. Indeed, we found that this pupil metric showed signatures of decision confidence based on signal detection theory: it increased with the animals' performance accuracy and was systematically associated with stimulus strength on correct and error trials. We then used this pupil size based metric to examine systematic effects of the animals' decision confidence on their perceptual strategy using psychophysical reverse correlation. While the animals' use of the stimulus over time averaged over all trials could not differentiate between weighted integration, adaptation or an integration-

to-bound, the difference in perceptual strategy for high versus low confidence trials supported an integration-to-bound strategy. Combining pupil size measurements and psychophysical reverse correlation provides a powerful tool to identify how an animal is solving a perceptual task. These insights are important when interpreting simultaneously recorded neural activity.

Disclosures: **K. Kawaguchi:** None. **S. Clery:** None. **P. Pourriahi:** None. **L. Seillier:** None. **R.M. Haefner:** None. **H. Nienborg:** None.

Poster

058. Visual Cognition: Decision Making

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Topic: D.07. Vision

Support: EY016774

Title: Decision signals in local field potentials recorded from early and mid-level visual cortical areas

Authors: *A. KRISHNA[1,2], S. TANABE[1], A. KOHN[1]
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Abstract: The neurophysiological basis of perceptual decision making has typically been studied using measurements from single neurons, though decisions are likely based on the activity of large ensembles of neurons. Local field potentials (LFPs) reflect the summed activity of neuronal populations and may serve as a proxy for population spiking activity. LFPs may also be sensitive to weak synaptic inputs which may be difficult to detect in spiking activity. Although these properties suggest the LFP would be useful for understanding the relationship between neural activity in different brains areas and animal's perceptual judgments, only a few studies have investigated whether LFPs in the primate visual cortex carry such information.
We measured LFPs using two 48-electrode arrays implanted in primary visual cortex (V1) and area V4 of macaque monkeys (*Macaca fascicularis*). Monkeys were trained to perform a fine orientation discrimination task, in which they indicated their decision as to whether the grating orientation was above or below 45° with a saccade to an appropriate target. We measured the average LFP power in gamma (30-70 Hz) and higher frequency bands (70-200 Hz and 200-500 Hz); before, during and immediately following stimulus presentation (before judgments were reported). We focused on responses to the ambiguous stimulus (45°), for which the monkeys were rewarded on 50% of the trials (randomly). To determine whether the LFPs contained choice-related signal we 1) used choice probability (CP) analysis, 2) employed a logistic regression decoder, trained to predict the decision of the monkey from LFPs recorded at multiple

electrodes.
We found significant single electrode CP in both areas. Choice-related activity was more evident in later epochs of the trial, than before or immediately following the stimulus onset. The magnitude and consistency of the CP values were greater at higher frequency bands compared to gamma. The population decoder was successful in predicting the monkey's choice above chance level in both areas. Decoder performance was best in higher frequency bands, and when applied to later epochs of the trial. Our analysis reveals the presence of choice-related signals in the LFPs recorded in V1 and V4, and suggests LFPs may be a useful complement to spike-based analysis of decision making.

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Poster

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Support: NIH Grant EY000404

Title: Time course of noise correlations is much slower than stimulus selectivity for macaque MT neurons presented with bistable stimuli

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Abstract: The orthographic projection of dots on the surface of a rotating cylinder produces a compelling 3-D percept that is bi-stable, undergoing spontaneous reversals. Appropriate horizontal disparities specify the rotation direction and render the stimulus unambiguous. We have previously shown that when monkeys judge the rotation direction of ambiguous cylinders, simultaneously measured noise correlations in Middle Temporal (MT) area strongly depend on the task axis (i.e., cylinder orientation). This suggests that much of the noise correlation in this task reflects feedback processes. If the correlations are generated by a process distinct from that producing stimulus selectivity, they may develop with a different time course. In addition, if Choice Probabilities (CPs) are related to noise correlations in the way described by pooling models, they should evolve with a time course no faster than the correlations. We therefore examined the time courses of noise correlations, CPs, and stimulus selectivity of MT neurons. On trials for which the animal reported rotation direction, the stimulus rotated about a fixed axis for 2 s, with one of 7 disparities (including zero). To estimate the variables of interest on a continuous time scale, spike trains of individual trials were smoothed with an exponential filter (50 ms time constant). For 2609 pairs of well-tuned neurons (456 cells, 2 monkeys), noise

correlations at each time point were averaged separately for pairs having the same sign of tuning and for those with the opposite signs. An exponential function was fit to instantaneous difference in the mean correlations between the two groups. Here and in subsequent analyses, the rise started 70 ms after stimulus onset, and the values prior to 70 ms were fit with a constant baseline. The fitted time constant was 108 ms (89-132 ms, 95% confidence interval (CI)). CPs developed significantly more slowly, with a time constant of 362 ms (320-414 ms, 95% CI). To examine selectivity for disparity-defined rotation we selected the disparities (with opposite signs) that produced the strongest and weakest responses, measured during separate trials requiring only passive fixation (stimulus duration 500 ms, data available for 370 cells). The difference between these responses rose with a time constant of only 18.5 ms (16.9-20.2 ms, 95% CI). This dissociation between the time course of stimulus-driven activity and noise correlations further supports the idea that the noise correlations are not simply inherited from afferent inputs.

Disclosures: I. Kang: None. **B.G. Cumming:** None.

Poster

058. Visual Cognition: Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 058.13/BB24

Topic: D.07. Vision

Title: Neural mechanisms of perceptual learning in frontal eye fields neural population

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Abstract: Perceptual learning improves accuracy of acting on sensory information. Previous studies linked learning to changes in sensory cortex, and more recently, to improved readout of sensory information by action-planning circuitry. However, insights from past studies are limited by task designs in which sensory stimuli varied along one dimension (e.g., motion direction or grating orientation). Consequently, we know little about perceptual learning in natural settings that involve multi-dimensional stimuli: How are different dimensions combined to learn a category boundary? What is the relative contribution of improved sensitivity and improved category boundary to perceptual learning? And, do the same neural mechanisms underlie both improvements? To address these questions, we trained macaque monkeys to categorize simple shapes that varied along two dimensions: width and height. We divided this 2D stimulus space into two categories with an arbitrary, linear boundary. On each trial, monkeys briefly viewed a shape from the stimulus space and after a short delay reported its category with a saccade to one of two targets. Monkeys learned the task by try and error, and generated threshold-level psychophysical behavior within a few days of training. As monkeys learned the task, we

recorded neural responses in the frontal eye fields (FEF) using axial multi-electrode arrays. We show that changes of behavior across sessions stemmed from (i) increased sensitivity to relevant stimulus dimensions and (ii) convergence of monkeys' subjective category boundary to the true one. These two mechanisms accounted for 40% and 60% of improved accuracy, respectively. Further, we show that FEF responses changed gradually, hand in hand with learning. First, choice predictive activity emerged earlier after stimulus onset on each trial as training progressed, indicating a transition from stimulus-independent actions in early stages of training to stimulus-based decisions in later stages. Second, in line with previous reports in lateral intra-parietal cortex, FEF neurons showed an amplified representation of stimulus strength (distance from category boundary) with training. Third, the inferred decision variable from population responses (Kiani et al, 2014) reflected both an overall increase in sensitivity to the stimuli and optimization of subjective category boundary. Critically, these effects were present during stimulus viewing and long before the saccade. Our results suggest that FEF is part of a frontoparietal circuit that interacts with visual cortices to implement various aspects of perceptual learning.

Disclosures: L. Sha: None. **R. Kiani:** None.

Poster

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McKnight Scholar Award

Whitehall Foundation Research Grant

Title: Predicting belief from accuracy in perceptual decisions

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Abstract: In perceptual decisions subjects infer hidden states of the environment based on noisy sensory information to obtain reward. This inference process yields both a choice and an expectation of success. Choices and their accuracy are usually easy to measure, but beliefs about the likelihood of success (confidence) are not readily accessible to experimenters, especially in

nonverbal animals, unless special and often arduous behavioral paradigms are employed. Here we show that it is possible to use a Bayesian framework to accurately predict subjects' confidence based on their accuracy for simple perceptual decisions. Our framework builds on a partially observable Markov decision process (POMDP). POMDPs assume that subjects optimize a reward function by adjusting their beliefs about stimulus identity and the best choice based on a sequence of sensory observations and prior knowledge about the probability distribution of sensory observations and environmental states. We show that one can infer these distributions from subjects' accuracy and simulate temporal propagation of belief through an appropriate POMDP. We demonstrate the accuracy of our predictions by testing them on the behavioral data of monkeys performing a random dots motion direction discrimination task with post-decision wagering (Kiani & Shadlen, 2009). On each trial monkeys observed a patch of random dots and after a short delay either reported motion direction by choosing one of two "direction" targets or bailed out of reporting the direction by choosing a "sure bet" target. The sure bet target was available on a random half of trials. Direction targets yielded a large reward only if they corresponded to the correct motion direction. The sure bet target yielded a small reward, regardless of the stimulus. Motion duration and strength (percentage of coherently moving dots) varied from trial to trial, changing task difficulty. Choosing the sure bet target provided a reliable estimate of monkeys' confidence for different difficulty levels. We used monkeys' accuracy on trials without the sure bet target to fit our POMDP and based on the model predicted wagering behavior on trials with the sure bet target. Our predictions matched the observed behavior. Moreover, compatible with the data, the beliefs generated by our POMDP exhibited the "hard-easy" phenomena, where subjects' confidence is higher than accuracy for hard trials, but lower than accuracy for easy trials. The ability to predict confidence based on accuracy offers a significant advantage for studying hidden states of the decision-making process without directly measuring them.

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Poster

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McKnight Scholar Award

Pew Scholarship in the Biomedical Sciences

Title: Frontal and parietal areas represent distinct processes supporting hierarchical decisions over different timescales

Authors: *B. PURCELL, R. KIANI
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Abstract: Goal-directed behavior in a natural environment depends on a hierarchy of interacting decision processes. A high-level strategy guides lower-level choices by establishing potential actions and expected outcomes for incoming stimuli. Selecting the right strategy is a decision too and informed by the expectations and outcomes of the lower-level choices. We recently showed that such hierarchical decisions guide behavior in dynamic environments where stimulus-response associations should change based on context: A lower-level process integrates evidence within a trial to compute choice and expected accuracy, while a higher-level process integrates expected accuracy and feedback across trials to compute the best strategy for future decisions. To study the neural mechanisms of these processes, we used multi-electrode arrays to simultaneously record spiking activity of neural populations in lateral intraparietal (LIP), supplementary eye field (SEF), and dorsolateral prefrontal cortex (DLPFC) of macaque monkeys performing a “changing environment” task. The task consisted of two environments, one of which was active for several trials and then switched to the other without explicit cue. On each trial, monkeys viewed a patch of random dots and after a short delay chose one of three targets: two direction targets (right and left) to report motion direction and a switch target to report an environment change. The switch target transitioned the monkey from one environment to the next and generated reward if the new environment was active. The direction targets generated reward if the current environment was active and the chosen target corresponded to motion direction. We changed the difficulty of motion discrimination by varying motion strength (coherence) and duration. Monkeys, like humans, were more likely to switch after negative feedback for easier direction choices. Further, they integrated negative feedback and expected accuracy across trials to decide on switching, as predicted by our computational model. The three frontoparietal regions represented the model sub-processes. LIP population responses showed a low-level decision variable (DV) for integration of motion within trials. SEF reflected this low-level DV but also represented a high-level DV for switching that depended on the history of feedback and expected accuracy, consistent with long-term integration in the model. In contrast, DLPFC maintained a representation of the current environment throughout multiple choices. Our results demonstrate how different areas may specialize to support distinct computations underlying sustaining and changing decision strategies.

Disclosures: **B. Purcell:** None. **R. Kiani:** None.

Poster

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Title: Extending models of latent dynamics in area LIP during perceptual decision-making

Authors: D. M. ZOLTOWSKI[1], K. L. LATIMER[2], A. C. HUK[3], *J. W. PILLOW[4]
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Abstract: The firing rates of neurons in the lateral intraparietal area (LIP) in macaques during visual perceptual decision-making tasks are correlated with perceptual evidence accumulation, but the latent dynamics underlying spike trains observed on single trials remain a matter of open debate. Recent analyses from (Latimer et al., 2015) compared models of single-trial latent dynamics in LIP with continuous diffusion-to-bound ("ramping") dynamics and discrete switching dynamics ("stepping"). Here we extended those models and analyses in several important directions. First, we examined the ramping and stepping model comparison using the Watanabe-Akaike information criterion (WAIC), a recent metric for Bayesian (sampling-based) inference that is suitable for comparing predictive accuracy of the models on a per-cell and per-trial basis. Second, we added spike history terms to both the ramping and stepping models to account for self-excitatory or self-inhibitory spiking behavior when identifying the underlying dynamics. We extended methods from (Latimer et al., 2015) to fit the models to the responses of 40 neurons from LIP during a random dot motion task (Meister et al., 2013) and to compute the WAIC. Using this metric, we found that the number of cells better described by the ramping or stepping model did not vary substantially when the models were fit to all of the trials or to only the nonnegative coherence trials. Also, we identified features of the data that the ramping and stepping models explained poorly using the per-trial WAIC. Second, we found that modeling spike history effects as a multiplicative gain on the firing rate improved the predictive capabilities of both the ramping and stepping models. Finally, we extended the continuous ramping model to incorporate a nonlinear linking function between a latent diffusion process and firing rate to test if a linear, accelerating, or saturating nonlinearity better accounts for the relationship between accumulation-like dynamics and spiking in LIP.

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Poster

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Topic: D.07. Vision

Support: NEI 1R01EY0251581

Title: LIP neurons encode cognitive effort associated with resolving conflict and obtaining information

Authors: ***M. HORAN**[1], N. DADDAOUA[1], J. GOTTLIEB[1,2]
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Abstract: Background
The fact that rewards modulate visual responses suggests that motivation impacts vision, attention and eye movements. In monkeys, lateral intraparietal (LIP) neurons that select targets for attention and gaze are sensitive to expected reward (ER), and have been proposed to encode the values of alternative options. However, in natural behavior attention is associated with a cognitive cost - the effort required to sample and process information. We recently showed that LIP neurons positively encode the expected information gains (EIG) of alternative visual cues, and EIG was associated with higher attentional effort as indexed by longer viewing durations. Here we extend this observation by asking how neurons combine signals of ER and EIG.
Method
Monkeys performed a 2-step decision task in which they made a first saccade to sample information from a visual cue and a second saccade to indicate a decision based on the information. Following a well-known motion discrimination paradigm, the information consisted of 100% coherent motion indicating which one of two alternative targets was correct. However, in contrast with traditional versions of this paradigm, we placed the cue in the receptive field of the LIP cells and delivered the motion instruction in a gaze-contingent fashion, only after the monkeys foveated the cue, allowing us separate responses to the saccadic decision from the post-saccadic motion discrimination. We manipulated EIG by contrasting trial blocks in which one target was a priori correct with those in which the two targets had equal probability of being correct. While in the former block type the monkeys made their final decision based on their prior knowledge of target location (and the cue merely brought redundant information), in the latter block the monkey started off with decision uncertainty and resolved that uncertainty by viewing the cue. Within high and low EIG blocks we further manipulated ER by interleaving

trials with small and large rewards, using the fixation point color to signal reward size.
Results
LIP neurons had enhanced pre-saccadic responses if the cue was associated with high relative to low EIG and, strikingly, if it was associated with a smaller rather than larger reward. As expected, trials with high EIG had longer viewing durations suggestive of higher attentional effort. Trials with lower rewards also had longer viewing durations produced by motivational conflict associated with the low-value saccade.
Conclusion
We propose that LIP neurons signal the recruitment of cognitive effort in decision making, whether effort arises from the need to resolve motivational conflict or reduce uncertainty by sampling information.

Disclosures: **M. Horan:** None. **N. Daddaoua:** None. **J. Gottlieb:** None.

Poster

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Topic: D.07. Vision

Support: HHMI

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DARPA

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Title: Frequency shifts and depth dependence of pre-stimulus beta band activity in rhesus premotor cortex during perceptual decision-making

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Abstract: Single neuron and local field potential (LFP) responses in the premotor and motor cortex show considerable, prominent structure in the beta frequency range (13-30 Hz) before movement onset. Currently, the role of beta band activity (BBA) in premotor cortex during perceptual decision-making is not well understood. Across several studies, there are two main hypotheses about the role of BBA, each with corresponding expected relationships between BBA and reaction time (RT): 1) BBA is a signal of attentional engagement and should be negatively correlated to RT, 2) BBA represents a willingness to maintain the current state of being and

should be positively correlated to RT. How BBA power changes as a function of cortical depth is also unknown.
We addressed these unresolved questions by investigating BBA recorded using laminar electrodes (U-probes, 16 contacts, 150 μm spacing) in the dorsal premotor cortex (PMd) of two male rhesus macaques performing a visual RT discrimination task with arm movements as the behavioral report. Over 37,009 trials (24 sessions) for Monkey T and 24,549 trials (17 sessions) for Monkey O, we observed robust BBA during the hold epoch prior to the visual stimulus (static checkerboard) of our decision-making task, both in the LFP and in spiking activity. We found that this pre-stimulus BBA was correlated with RT. By examining frequencies independently (rather than averaging over large frequency ranges), we found that correlations were positive (maximum $r = 0.062$, $p = 1.73 \times 10^{-8}$) for the low beta frequencies (~15 to 20 Hz) and negative (minimum $r = -0.080$, $p = 3.29 \times 10^{-4}$) for the high beta frequencies (~25 to 30 Hz). This result is consistent with other reports of frequency-dependent correlations with RT (Zhang et al., JOCN, 2008). Through simulations, we show that the observed frequency-dependent correlation is consistent with a shift in the frequencies of the pre-stimulus BBA as a function of RT (Kilavik et al., Cereb Cortex, 2011), such that pre-stimulus BBA with more power in the low BBA frequencies is associated with slower RTs. We also observed a laminar dependence of BBA, with low beta frequencies showing greater power in deeper cortical layers.
Our results showing positive correlations for low beta and negative correlations for high beta support both the maintenance of current state hypothesis and the attentional hypothesis respectively. Frequency shifts for BBA may reflect top-down attention, bottom-up somatosensory inputs in the decision-making task and other elements such as arousal. Additionally, the changes in BBA as a function of cortical depth may arise due to inputs from other brain areas and/or differences in local network dynamics in PMd.

Disclosures: **I.E. Bray:** A. Employment/Salary (full or part-time):; Stanford Electrical Engineering REU Program-VPUE. **C. Chandrasekaran:** 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/NINDS K99/R00 grant NS092972. **K.V. Shenoy:** Other; Neuralink Inc., consultant, Cognescent, Scientific Advisory Board, Heal, Scientific Advisory Board.

Poster

058. Visual Cognition: Decision Making

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Title: Using action potential width and cortical depth to characterize laminar microcircuit organization in macaque dorsal premotor cortex during perceptual decisions

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Abstract: The dorsal premotor cortex (PMd) is implicated in choosing and performing actions based on sensory cues. However, we currently lack an understanding that can be used to build anatomically-guided computational models. We previously showed that a diverse neural population in PMd covaries with the decision-formation process and that some of this diversity is subsumed by the laminar organization in PMd (Chandrasekaran et al. SFN ‘14, ‘15). Here we examined if putative cell type as characterized using action potential (AP) waveform width and shape could help further understand this diverse neural population in PMd.
We report here 552 neurons recorded in PMd using linear multi-contact electrodes (16 electrodes spanning 2.4 mm) while 2 monkeys performed a visual reaction time (RT) reach decision-making task. These PMd neurons can be organized into three broad categories using a bidirectional visuomotor continuum. The Increased neurons at the positive end of the continuum increased their FRs ~150 ms after visual stimulus onset, and these FRs covaried with choice, stimulus difficulty, and RT—properties expected of a candidate decision variable. Increased neurons were more common in the superficial cortical depths. The Decreased neurons at the opposite end of the continuum decreased their FR after visual stimulus onset. For the Perimovement neurons at the center of the continuum, FRs were unmodulated early in the trial, with modulations appearing only ~150 ms before movement initiation. These Decreased and Perimovement neurons did not show decision-variable like characteristics and were more common in deeper cortical depths.
We further delineated the laminar microcircuit in PMd by examining the relationship between AP width, cortical depth, and visuomotor index. We found that AP waveforms in deeper cortical depths were either broad (> 200 μs, putative excitatory neurons), or triphasic and very narrow (< 100 μs, putative axons). In contrast, AP waveforms of neurons in superficial cortical depths were biphasic in shape and narrower in width (putative inhibitory neurons, ~100-200 μs). We found a

significant relationship between waveform width and the visuomotor index ($r=-0.12$, $p < 0.006$) even when we controlled for cortical depth. Visuomotor index was still correlated to cortical depth even when controlling for AP width ($r=-0.19$, $p < 1.3e-4$). Our results are some of the first demonstrations of an organization of AP width as a function of cortical depth and a laminar organization for decision-related responses. These results, which are consistent with anatomical hypotheses, inform and guide the design of anatomically-grounded computational models of decision-making.

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Poster

058. Visual Cognition: Decision Making

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German Research Foundation (DFG), DO 1240/3-1

German Research Foundation (DFG), SFB 936/Z

Title: Multiplexing of arousal-linked top-down signals in early visual cortex

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Abstract: Early visual cortex does not respond passively to the sensory environment, but its state is strongly shaped by top-down factors. Previous work has identified top-down signals in visual cortical population activity related to task structure, spatial attention, or behavioral choice. These signals have not been compared directly within a single experiment. Here, we identified functionally distinct top-down signals in human visual cortex during a visual decision task. We also quantified their dependence on phasic arousal boosts (indicated by pupil dilation), which are reliably evoked during perceptual tasks and are thought to be an important factor governing rapid changes in cortical state.
15 human subjects performed a yes-no contrast detection task near 75% correct detection threshold, during concurrent fMRI and eye tracking. They viewed a continuous stream of dynamic black and white noise centered around the fixation mark on a gray background. Each

trial started with an auditory cue, followed by one of two stimuli: a low-contrast grating superimposed onto the noise ('signal+noise', 50% of trials, 25% clockwise, 25% counter-clockwise orientation), or a continuation of the same noise ('noise trials'). Subjects reported their yes-no judgment about signal presence with a button press.
The stimulus-responsive sub-regions of visual cortical areas V1-V3 exhibited fMRI responses during the trial, which were spatially specific (not evident in the surround), and equally strong on signal+noise and noise trials. Because noise trials did not contain any change in the visual stimulus, we reasoned that this fMRI response was a top-down signal related to spatial attention, as observed previously (Ress et al, *Nat Neurosci*, 2000). Multi-voxel pattern analysis delineated two further functional components of the V1-V3 population response: (i) an orientation-tuned response and (ii) a decision-related signal. The orientation-tuned response encoded signal presence, but not behavioral choice. Conversely, the decision-related signal encoded choice, but not signal presence. Trial-to-trial variations in pupil-dilations were correlated with the attention- and decision-related components, but not the orientation-tuned response. All three signal components were spatially distinct from one another.
The results indicate that two distinct top-down signals, related to spatial attention and behavioral choice, can coexist with an orientation-tuned sensory response during contrast detection in early visual cortex. Both top-down signals are boosted by pupil-linked phasic arousal, suggesting that arousal can sculpt selective cortical population signals.

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Poster

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Support: KAKENHI(16H01866)

KAKENHI(26560325)

Title: Neural correlates for judgment of visual pattern randomness: An event-related potential study

Authors: *T. MIYAGI[1], H. FUJIMURA[2], T. KURODA[2], Y. YAMADA[3], K. KANNAGA[2], S. TAKEUCHI[4], M. MIYAZAKI[2]
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Abstract: After prolonged exposure to visual dot patterns with high or low levels of physical randomness, perceived randomness eventually decreases or increases, respectively (Yamada et al. 2013, *Sci Rep* 3: 2906). The pattern randomness aftereffect is non-selective to the contrast polarity of visual patterns; however, it is selective to the orientations of the patterns. On the basis of these psychophysical properties of pattern randomness aftereffect and previous neurophysiological findings (Murray and He 2006, Lerner et al. 2002, Kourtzi et al. 2003), Yamada et al. (2013) predicted that the lateral occipital complex (LOC) is involved in the perceptual processing of visual pattern randomness. In this study, using electroencephalography (EEG), we detected the neurophysiological responses during judgment of visual pattern randomness. While EEG signals were recorded from 63 scalp electrodes (10-10 system), participants (N = 20) performed randomness judgment (RJ) and contrast judgment (CJ; control task) for identical visual patterns. The EEG signals were digitized continuously at 1000 Hz. EEG data were re-referenced offline to Nz and bandpass filtered at 0.053-15 Hz. Event-related potentials (ERPs) were calculated separately for RJ and CJ by averaging the EEG signals time-locked to the target visual patterns, relative to a 200-ms pre-stimulus baseline. The grand average ERPs for RJ exhibited a higher positive peak (latency of 97 ms) than those for CJ, over the left lateral parieto-occipital scalp areas (prominent around PO7). The mean ERP amplitude in a 20-ms time range centered on the positive peak at PO7 was significantly larger for RJ than for CJ (P = 0.028). At the later stage (after latency of 200 ms), ERPs for RJ revealed higher sustained positive activity than those for CJ over the parietal and frontal scalp areas. The mean ERP amplitudes at CP3 and CP4 during latency of 220-600 ms were significantly larger for RJ than for CJ ($P < 0.001$). The mean ERP amplitude at FC4 during latency of 230-600 ms was significantly larger for RJ than for CJ (P = 0.005). The early RJ-related positive peak at PO7 probably reflects the perception-related activity of the LOC (cf. Takeya et al. 2014), which is consistent with the prediction by Yamada et al. (2013). The later RJ-related positive sustained activity recorded from the parietal and frontal scalp areas is likely associated with the cognitive or integrative processes for pattern randomness judgment.

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Poster

058. Visual Cognition: Decision Making

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Title: Differing timescales of interneuronal correlations contribute to differences in decision signals in area V5/MT; comparing a stereo-motion task with random motion stimulation

Authors: *D. F. WASMUHT, A. J. PARKER, K. KRUG
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Abstract: How external stimuli give rise to perceptual decisions has been proposed to depend on the correlated activity of groups of behaviorally relevant neurons in the primate brain. Here, we quantify inter-neuronal correlations (spike count correlations) between neurons, their time course and perceptual choice signals in visual area V5/MT of two macaques. Single unit and surrounding multi-unit activity were recorded from the same electrode while the monkeys made perceptual decisions about the direction of rotation of a structure-from-motion cylinder, which requires the specific combination of 3D depth and motion to disambiguate perceptual appearance. Across all recorded sites (n=61), the average spike count correlation evoked by a perceptually ambiguous cylinder stimulus was high at r=0.28. When pseudo-randomly interleaved with a zero-coherence motion stimulus and selecting for sites with fully matched disparity and motion tuning preferences (DDI>0.1), correlation values for the ambiguous cylinder were significantly larger than for random dot motion (0.4 vs 0.22, n=28, paired t-test on fisher's z $p<0.01$). Observed values for spike count correlations rose as a function the strength of a neuron's tuning curves to motion direction and cylinder rotation. Analysis of the time-scale of correlations revealed that the difference in correlations between the two stimulus paradigms arose at large timescales (hundreds of milliseconds). Correlations evoked by non-ambiguous versions of the cylinder were significantly smaller than those for the ambiguous version (0.29 vs 0.23, n=61, $p<0.05$, approaching the correlation value evoked by random motion stimuli (0.23 vs 0.19, n=32, p=0.33). Focusing on ambiguous cylinder stimuli, we found a positive correlation between the spike count correlations of neurons and their choice-related activity (choice probability) (Pearson's r=0.37, n=38, $p<0.05$). Large choice probabilities were specifically associated with correlations at large time scales (hundreds of milliseconds). Additionally, we found that the time course of choice probabilities was predicted by the time course of correlations on larger timescales but not the instantaneous correlations. Our results suggest that enhanced values of spike count correlation and choice probability for the ambiguous cylinder are the neural signature of top-down influences into V5/MT processing, which could convey and stabilize the signals that shape the perceptual appearance of visual stimuli.

Disclosures: D.F. Wasmuht: None. **A.J. Parker:** None. **K. Krug:** None.

Poster

058. Visual Cognition: Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: D.07. Vision

Support: Strategic fund for the partnership between Newcastle University and Monash University

FT130101488 Australian research council

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093104 Wellcome trust

Title: Behavioural and neural signatures of decision making vary with pupil diameter and clonidine administration

Authors: *J. VAN KEMPEN[1], D. P. NEWMAN[2], G. LOUGHNANE[4], S. KELLY[5], A. THIELE[1], R. O'CONNELL[4], M. A. BELLGROVE[3]
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Abstract: Decision making depends on the temporal accumulation of evidence. This accumulation process relies on both external influences, such as the strength of the signal, as well as internal factors, such as arousal. Pupil diameter increases during effortful decision making, mediated by neuromodulatory systems that also influence global brain state. Classically, pupil diameter is thought to reflect locus coeruleus (LC) noradrenergic (NA) functioning, mirroring both the tonic and phasic activity seen during task (dis)engagement. LC activity has been related to the outcome of the decision process and is hypothesised to synchronise distant brain regions to facilitate behavioural responses. However, increasing evidence suggests that pupil diameter may also reflect the evidence accumulation process itself, although neurophysiological data to support this claim have been lacking. Here we tested how baseline pupil diameter and pupil dilation relate to electroencephalographic correlates of decision making during a random dot motion detection paradigm. In the first experiment, we found that pupil diameter predicted response times, pre-target attentional engagement (indexed by occipital α desynchronisation) and both the onset and slope of the neural evidence accumulation process (indexed by the Centro-Parietal Positivity, CPP). In a second experiment we tested the effects of clonidine, an α2 adrenergic agonist which at low doses acts presynaptically to inhibit the release of NA, on these same neural signatures. We found that compared with placebo, clonidine

affected pupil diameter, reaction times, pre-target occipital α synchronisation and the onset, but not the slope, of the CPP decision signal. These results reveal the relationship between pupil diameter and the neural correlates of decision making and how these signatures are influenced by NA drug application.

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Poster

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James S McDonnell Foundation

Medical Research Service of the Department of Veterans Affairs 5I01CX000359

NIMH 24600

Title: Effects of attention and expectation on perceptual decision making after medial temporal lobe lesions

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Abstract: Top-down factors such as attention and expectation have been shown to improve decision making. In an earlier study, we found that both attention and expectation influence the accumulation of sensory evidence via different mechanisms. In particular, attention increases the rate at which sensory evidence is integrated in the time leading up to a decision. In contrast, expectation about stimulus probability induces a pre-stimulus response bias towards a decision choice associated with the more likely stimulus. Past studies involving a single patient have implicated the medial temporal lobe, including the hippocampus, in detection and extraction of temporal regularities of the sensory input in the environment (e.g., Schapiro et al., 2014). Here, we evaluated whether the medial temporal lobe is also necessary for expectation-induced improvements in perceptual decision making when the predictability of stimulus features are systematically manipulated. Additionally, we examined whether the attentional effect on decision making in this context is hippocampus-dependent. In the present study, a group of memory-impaired patients with medial temporal lobe damage and eleven controls were

presented with a display of moving dots, half of which were black and half of which were white. On each trial, some percentage of the dots was rendered to move in the same direction. We manipulated attention (behavioral relevance) by cueing participants to monitor either the black or white dots (focused attention) or to monitor both (divided attention). Expectation of the target-defining motion direction was also manipulated by varying the ratio of targets rendered in a particular direction during different blocks of trials. Participants were instructed to indicate their response using a flight-simulator joystick. We examined the effects of attention and expectation on patient decision making by evaluating their response trajectories and response errors as a function of these two manipulations. Preliminary results suggest that both attention and expectation improve decision making in patients as much as in controls. Particularly, attention increases the rate at which sensory evidence accumulates, whereas expectation biases the pre-stimulus response leading to an increase in performance accuracy.

Disclosures: **N. Rungratsameetaweemana:** None. **L.R. Squire:** None. **J.T. Serences:** None.

Poster

058. Visual Cognition: Decision Making

Location: Halls A-C

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Topic: D.07. Vision

Support: Funding for this study was provided by the Office of Naval Research to Aptima, Inc.

Title: Evaluating the impact of expertise on intuitive decision-making: A neurocognitive study

Authors: *L. C. LUCIA, J. M. BEAUBIEN, E. W. STACY
Aptima, Inc., Woburn, MA

Abstract: Military missions pose complex cognitive and perceptual challenges, such as detecting potential improvised explosive devices along the roadside, and/or detecting anomalous social cues in a crowded market suggestive of an impending attack. Situations such as these do not allow time for extensive deliberation. In fact, the ability to make quick and accurate decisions based on implicitly perceived cues (i.e., intuitive decision-making) is key to survival in such situations. Unlike deliberate decision-making, intuitive hunches develop quickly and are considered largely automatic (Cannon-Bowers et al., 1997). Neurocognitive research has begun to shed light on the neural mechanisms underlying intuition. For example, Luu and colleagues (2010) used electroencephalography (EEG)-based techniques to identify a neural correlate of intuition during an object recognition task. The purpose of the current study was to expand on past work and examine the generalizability of this neural signal within a military context (e.g., submariners performing a task relevant to their domain of expertise: periscope operations). The study included a mix of 27 novice and expert submariners, and used a rigorously controlled

within-subjects experimental design. Statistical analyses of the participants' ERPs, reaction times, and accuracy measures provide evidence for generalized markers of intuition, and suggest that these markers can differentiate between the accurate decision-making performance of expert submariners from the less accurate performance of novices. Further, through Diffusion Analysis (which evaluates performance as a combination of response time and accuracy; Ratcliff & Turelinckx, 2002), results revealed experience-dependent variations in the perceptual, cognitive, and motor planning processes involved in the task. Overall, electrophysiological and performance results suggest that processes of selective attention and perceptual hypothesis testing are enhanced in experts compared to novices, and this is what contributes to their enhanced intuitive decision-making performance.

Disclosures: L.C. Lucia: None. **J.M. Beaubien:** None. **E.W. Stacy:** None.

Poster

058. Visual Cognition: Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 058.26/CC10

Topic: D.07. Vision

Support: MH095984

Title: Confidence amplifies serial dependence in perceptual decisions

Authors: *J. SAMAHA, M. SWITZKY, B. R. POSTLE
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Abstract: Over a century of psychophysical research has implicitly relied on the assumption that perceptual decisions are causally related to only the stimulus presented on the current trial. Recent research, however, has shown that stimuli seen several seconds prior, on a previous trial, can influence decisions about the current stimulus, a phenomenon known as *serial dependence*. Here, we investigated whether this effect was mediated by the observer's subjective sense of confidence in the decision from the previous trial. We found that orientation decisions on the current trial were more strongly biased towards the previous trial's orientation when the previous trial was perceived with high confidence. Crucially, a further manipulation that boosted confidence without changing task performance also led to the same effect, indicating that increased confidence, in and of itself, was sufficient for amplifying the impact of the previous trial on the current trial's decision. In other words, this effect was not merely due to the fact that confidence typically correlates strongly with task performance. Mechanistically, serial dependence may be driven by residual neural activity in attractor networks with slow time constants, suggesting that confidence may mediate the rate of decay of information in such networks. Or, confidence may boost the overall activity in the population representing the

previous trial's stimulus such that this activity takes longer to return to baseline and can more readily influence decision making on the current trial. Because prestimulus oscillations in the alpha-band (8-13 Hz) are known to predict trial-to-trial variation in confidence, the current results suggest that the oscillatory state of spontaneous brain activity on previous trials can have distal effects on the current trial's decision. Regardless of mechanism, these results suggest that subjective confidence functions to enhance the perceived continuity of the visual environment.

Disclosures: J. Samaha: None. **M. Switzky:** None. **B.R. Postle:** None.

Poster

058. Visual Cognition: Decision Making

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Support: MRC intramural Grant MC-A060-5PQ30

Wellcome Trust

James F McDonnell Foundation

Title: From perception to action in an uncertain world: Decisions all the way with beta desynchronization

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Abstract: Normal behaviour requires one to evaluate sensory information and select an appropriate response. Perceptual decisions are made by the accumulation over time of sensory evidence until a threshold is reached (Gold & Shadlen 2007). Action selection may proceed by an analogous process in which motor intentions are accumulated to a response threshold (Rowe et al 2010). We examined the temporal dynamics and functional anatomy of the accumulators of sensory evidence and motor intentions by varying uncertainty in stimuli and response options respectively. The task used an array of 4 random dot kinematograms (RDK). After an interval of random motion, coherent downward motion appeared with high or low coherence (low/high perceptual uncertainty), in one or three RDK indicating available responses. Subjects pressed the button corresponding to a single coherent RDK (low action uncertainty) or chose one of three available options (high action uncertainty). We modeled the task using linear ballistic accumulators (LBA). Magnetoencephalography (MEG) was used to identify the spatiotemporal profile of the physiological correlates of the accumulation of sensory evidence and action

intentions. Shorter reaction times (RT) for low vs high perceptual and action uncertainties confirmed the efficacy of task manipulations. We fitted a series of LBA models with different free parameters to the distributions of RT. Model evidences showed that changes in the sole drift-rate parameter (i.e. accumulation speed) across conditions best describes the RT data. Drift-rates were slower for low vs high uncertainty in both perceptual and action decisions for each subject. The time-frequency representations of response-locked MEG activity revealed that desynchronization in the beta (13-30Hz) range is associated with high perceptual and action uncertainty. Differences in prefrontal and posterior brain regions accord with previous work in perceptual and action decisions (Donner et al 2009). However, the temporal profile of beta desynchronization differs between types of decision: Perceptual uncertainty ceases to influence desynchronization at ~300ms from response while the impact of action uncertainty lasts until response. These findings draw a distinction between perceptual and action stages of decision making, with sensory evidence accumulated before being mapped onto a motor plan, and action units competing until selection of a response.

Disclosures: **A. Tomassini:** None. **D. Price:** None. **J. Zhang:** None. **J.B. Rowe:** None.

Poster

058. Visual Cognition: Decision Making

Location: Halls A-C

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Program#/Poster#: 058.28/CC12

Topic: D.07. Vision

Support: ERC Parietalaction

Title: Not all observed actions are perceived equally

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Abstract: Although the exact taxonomy of human actions is far from firmly established, distinctions between observed action (OA) classes become increasingly clear, in particular that they are processed in different parts of human PPC. The present work builds on this notion, demonstrating that perception of observed actions differs between classes. We conducted 2 experiments in which two groups of 10 subjects discriminated in a 2AFC between videos depicting different versions of two action exemplars belonging to the same class. By scrambling a percentage of randomly chosen dot-pixel pairs in each video pair, we set signal strength at levels between 0 to 100%. In one experiment, we assessed subjects' performance in discriminating between a pair of skin-displacing actions, and in the other, between locomotion actions. These action classes were chosen because they activate very different regions in PPC

(Abdollahi et al., Cerebr Crt, 2013; Ferri et al., Hum Br Mapp, 2015) and involve very different typical effectors. The accuracy and response time were well fit by proportional rate diffusion model with 3 parameters (bound, drift rate and residual time) with threshold ratio being close to 3.5 (characteristic for diffusion models). The parameters and thresholds were compared between two action classes tested and the class of manipulative hand actions reported earlier (Platonov and Orban, Sci Rep, 2016). The diffusion model applied to multiple OA classes. More importantly, the observers' ability to discriminate exemplars of action classes differed amongst classes (one-way ANOVA: $F_{2,52}=13.03$, $p<0.01$). The parameter bound drove between-class differences (one-way ANOVA: $F_{3,33}=20.5$, $p<0.01$), while drift rate was responsible for inter-subject variations within each action class with significant negative modulation of the accuracy thresholds by drift rate in skin displacing ($r= -0.84$, $p<0.01$), locomotion ($r= -0.91$, $p<0.01$) and manipulative hand ($r= -0.68$, $p<0.05$) action discrimination. This is remarkable, as the parameter bound so far has only been changed by explicit speed accuracy trade-off manipulations. We propose that differences in bound values may result from the ecological validity of action videos compared to mostly artificial stimuli used in earlier studies, and is implemented by different levels of urgency signals originating in the PPC regions processing different OA classes.

Disclosures: A. Platonov: None. **G.A. Orban:** None.

Poster

058. Visual Cognition: Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 058.29/CC13

Topic: D.07. Vision

Title: Exploration of different processes in synesthetic bidirectionality

Authors: *J. F. AWAD[1], B. C. HACKNEY[2], R. MORALES[3], T. DOTY[3], R. L. MOSHER[5], S. A. DREW[4]
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Abstract: Grapheme-color synesthesia is a phenomenon marked by graphemes eliciting color experiences in an individual. This condition has typically been seen as a unidirectional experience, where the grapheme elicits color but the color does not elicit a grapheme. However, there are a growing number of studies supporting the notion of bidirectionality in grapheme-color synesthesia, with color eliciting grapheme perception. The findings from our previous study in this area supported the notion of colors eliciting magnitude for number-color synesthetes. Inclusion of participants' reaction times from the forced-choice magnitude task affords further investigation of whether color perceptions are elicited through memory or through

pre-attentional cues. When observing differences between reaction times for 2 and 3 digit stimuli (in which digits were represented by color patches), no significant difference was found. This suggests that memory is not playing a role in completing the task, providing direction to investigations of the different processes that elicit synesthetic experiences.

Disclosures: **J.F. Awad:** None. **B.C. Hackney:** None. **R. Morales:** None. **T. Doty:** None. **R.L. Mosher:** None. **S.A. Drew:** None.

Poster

059. Eye Movements: Smooth Pursuit

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 059.01/CC14

Topic: E.01. Eye Movements

Support: ERC Grant Position

Fondation pour la Recherche Medicale

Fondation de France : Berthe Fouassier

CNRS

Title: Cerebellar control of the ability to track a moving target: Role of the fastigial oculomotor region

Authors: ***C. BOURRELLY**[1,2], J. QUINET[1], P. CAVANAGH[3], L. GOFFART[4]
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Abstract: The fastigial oculomotor region (FOR) is the output nucleus by which the medioposterior cerebellum influences the generation of saccades. Its contribution to visual tracking is not yet completely understood. We investigated this question in two head-restrained monkeys by analyzing the effect of its unilateral inactivation on the interception and tracking of a moving visual target. Initially stationary for a variable duration, a central target then moved centrifugally along a cardinal or oblique axis, with a constant (10°/s, 20°/s or 40°/s), accelerating (from 0 to 40°/s) or decelerating (from 40 to 0°/s) speed. We describe here the effects of FOR inactivation on the eye movements during the horizontal (left vs right) target motions. After unilateral inactivation with muscimol, the tracking was smoother during ipsilateral target motions than during contralateral ones. During ipsilesional tracking, the interceptive saccade was hypermetric for all tested speeds. The targeting error was larger for the faster target. The gain of the post-saccadic pursuit was variable and not correlated with the change in saccade accuracy.

During contralesional tracking, both the amplitude of interceptive saccade and the gain of post-saccadic pursuit were reduced. This hypometria and the slowing of pursuit increased with the target speed. However, no correlation was found between the change in saccade accuracy and the change in pursuit eye movement. Depending upon the experiment, the magnitude of the impairments differed between the ipsilesional and contralesional saccades. However, within the same experiment, correlations were found between the deficits measured between different tested speeds. Together these results support the conjecture that different populations of neurons in the FOR are involved in controlling the accuracy of ipsilateral and contralateral saccades (Goffart, Quinet & Bourrelly, SFN 2017). Furthermore, for both the ipsilesional and contralesional tracking, the absence of correlation between the saccade dysmetria and the change in pursuit velocity indicate that the alteration of the FOR integrity has repercussions on the saccade and pursuit premotor systems through independent channels.

Disclosures: **C. Bourrelly:** None. **J. Quinet:** None. **P. Cavanagh:** None. **L. Goffart:** None.

Poster

059. Eye Movements: Smooth Pursuit

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Topic: D.09. Visual Sensory-motor Processing

Support: IBS-R015-D1

IBS-R001-D1

Title: Trial-by-trial correlations between multivariate EEG activity and smooth pursuit eye movements

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Abstract: Probing the neural origins of trial-by-trial variation in sensory-motor behavior is an important approach to understanding the neural mechanisms of sensory-motor transformation. Earlier studies on rhesus macaques have provided evidence for a sensory source of behavioral variation through a careful analysis of motor behavior and trial-by-trial correlations between neural and behavioral responses. However, attempts to identify the neural sources of trial-by-trial variation in human sensory-motor behavior were scarce. To understand the neural signals underlying the trial-by-trial variation observed in human sensory-motor behaviors, we asked the human subjects to track visual motion stimuli that randomly moved in one of five directions (pre-determined central direction, $+30^{o}$, $+60^{o}$, -30^{o}, -60^{o}). We recorded eye positions using an

infrared eye tracking device (EyeLink 1000 Plus, Brain Products, GmbH). EEG data were band-pass filtered into 5 frequency bands (Delta, Theta, Alpha, Beta, Gamma) and Hilbert-transformed. We decomposed the eye movement velocity traces into three components (latency, speed and direction), and applied a multiple linear regression analysis to find specific frequency-band activities that best predicted the trial-by-trial variation of each behavioral component. Our preliminary results suggest that the direction and latency variation of smooth pursuit eye movements can be predicted by the variation of the spatially distributed alpha and gamma band activity, respectively.

Disclosures: **W. Jeong:** None. **S. Kim:** None. **Y. Kim:** None. **J. Lee:** None.

Poster

059. Eye Movements: Smooth Pursuit

Location: Halls A-C

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Program#/Poster#: 059.03/CC16

Topic: E.01. Eye Movements

Title: Visual transient onsets decrease initial smooth pursuit velocity and reset the temporal dynamics of catch-up saccades

Authors: *A. BUONOCORE, Z. HAFED
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Abstract: Smooth pursuit eye movements allow us to track moving targets, and they synergistically interact with catch-up saccades to minimize foveal errors during such tracking. While smooth pursuit and saccades share several neural control mechanisms, the details of these mechanisms are still not fully resolved. In three experiments, we explored the effects of visual transient onsets on smooth pursuit initiation and the temporal dynamics of catch-up saccades. In Experiment 1, human participants followed a small target that started moving from screen center towards one of the four cardinal directions at ~27 deg/s. After 44-176 ms from target motion onset, we briefly presented a high-contrast 1-deg square for ~11 ms either ~8 deg in front of or behind the instantaneous target position. Experiment 2 used a similar paradigm except that we used a step-ramp target motion trajectory to minimize the occurrence of catch-up saccades during smooth pursuit initiation. During smooth pursuit initiation without an early catch-up saccade (Experiment 2), we observed a clear decrease in initial smooth pursuit eye velocity when visual transients were presented during the preparatory part of smooth pursuit (i.e. up to ~60 ms after motion onset) compared to when the transients were presented much later in time (i.e. >120 ms after motion onset). Interestingly, when aligning initiation catch-up saccade times to transient onset times in Experiment 1, we also found a strong reduction in saccade frequency compatible with the well-known phenomenon of saccadic inhibition. In Experiment 3, we extended the saccadic effects to sustained portions of smooth pursuit. We tested two rhesus macaque monkeys

tracking a target moving horizontally at ~14 deg/s. This time, the visual transient came at a random time during the entire pursuit duration, again either in front of or behind the instantaneous target position. We found similar results to those observed during pursuit initiation, supporting the hypothesis of a temporal resetting mechanism time-locked to visual transient onset, and affecting both the saccadic and smooth eye velocity control systems. Based on the effects that we observed on saccade-free pursuit initiation in particular, we specifically hypothesize that any neural locus that is uncovered for saccadic inhibition would also impact smooth pursuit eye movements.

Disclosures: **A. Buonocore:** None. **Z. Hafed:** None.

Poster

059. Eye Movements: Smooth Pursuit

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Topic: E.01. Eye Movements

Support: EY019266

EY006069

Title: Smooth pursuit adaptation affects the latency of catch-up saccades

Authors: *S. ONO[1], M. J. MUSTARI[2]
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Abstract: Smooth pursuit eye movements allow us to maintain the image of a moving object on or near the fovea. Catch-up saccades are often employed during smooth pursuit to maintain tracking quality. Adaptation of smooth pursuit and catch-up saccades are thought to be supported by different underlying mechanisms. However, it is still uncertain whether both position error and retinal slip signals during pursuit adaptation influence triggering catch-up saccades. The aim of this study was to determine the effects of smooth pursuit adaptation on concomitant catch-up saccades. It is known that the smooth pursuit system has the capability to adapt to changes associated with new behavioral demands. Therefore, we used a double-velocity step adaptation paradigm with two different velocities of target speed during a step-ramp tracking task. During an early adaptation period, the monkey used a combination of pursuit and catch-up saccades to keep his eyes on the moving target. In contrast, after adaptation of pursuit eye velocity, the number of catch-up saccades was reduced. We also found that the latency of the first catch-up saccades was significantly decreased following pursuit adaptation. This was the case even though position error 100ms before saccade onset was reduced. Our results indicate that catch-up saccades are triggered by relatively small position error and retinal slip following adaptation.

Therefore, even though there is some separation in circuitry for pursuit and saccades, adaptation of smooth pursuit speed affects the threshold for catch-up saccades.

Disclosures: S. Ono: None. **M.J. Mustari:** None.

Poster

059. Eye Movements: Smooth Pursuit

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Topic: E.01. Eye Movements

Support: ERC starting grant (677819 — BBRhythms)

Title: Microsaccades as fixational eye movements? On the influence of smooth pursuit eye movements and retinal input on microsaccades

Authors: *B. F. HANDEL[1], L. CAO[2], P. FRIES[3]
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Abstract: Microsaccades (MS) seem of janiform nature, because on the one hand, they are involuntary movements, i.e. they can be suppressed to a certain extent but not be voluntarily elicited; and on the other hand, they seem to be readily influenced by cognitive factors like attention. MSs have often been referred to as fixational eye movements, because they occur, when eyes fixate on a target. However, this notion is incomplete. Work by L. Jie (2007) suggests that MSs also occur during eye movements such as smooth pursuit (SP). Since this earlier study is based on a low sample size (n=7), we first aimed to replicate those findings. We then investigated possible factors that might influence the rate of MSs as well as the size and direction of MSs during SP. We measured 26 subjects with a 1000 Hz binocular eyetracker in an SP task: A visual grating stimulus (with a pursuit target in the center) was presented, which moved horizontally at one of two speeds or was static. The grating within the stimulus would independently move horizontally either to the left or right side, or be static. The task was to detect a color change of the grating in 20% of the trials, i.e. attention was not directed to the movement. The analysis window was 1 sec long, starting 500ms after pursuit onset. We find that MSs indeed occur during SP and that there is a significant overall bias of MS occuring in the direction of pursuit, i.e. opposite to the direction of retinal motion (rmANOVA, $p = 0.0003$; $F = 17.2$). In addition, the speed of SP is significantly associated with the number of those directed MSs (post-hoc ttest: each step in speed with $p < 0.00005$) but not the amplitude. When looking at the influence of the grating motion during fixation, we find a directional influence opposite to the direction of grating movements, i.e. in the direction of retinal motion (rmANOVA, $p = 0.01$; $F = 7.5$.). This influence, besides being in the opposite direction, is also

weaker than the influence of SP. The overall rate of MSs stayed constant over direction and speed conditions. If looking either at SP trials or fixation trials, surprisingly, the overall rate of MS is higher during SP compared to fixation despite identical retinal input (t-test, p=2.7 e-6, t=6). Our work shows that MSs indeed occur during SP and are influenced by the direction of these slow eye following responses. This influence is independent of the visual/retinal input and adds to our understanding of the underlying control mechanisms of MS.
Clark, James J., Ziad M. Hafed, and Li Jie. "Attention and action." Computational vision in neural and machine systems (2007): 129-148.

Disclosures: **B.F. Handel:** None. **L. Cao:** None. **P. Fries:** None.

Poster

059. Eye Movements: Smooth Pursuit

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 059.06/CC19

Topic: E.01. Eye Movements

Support: NSERC

CFI

Title: A Bayes optimal decision model of the saccade trigger mechanism during smooth pursuit

Authors: *J. COUTINHO[1], P. LEFÈVRE[2], G. BLOHM[1]
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Abstract: Accurate visual tracking depends on the synergistic control of smooth pursuit and saccadic eye movements. Pursuit eye movements are controlled primarily by retinal image velocity (‘retinal slip’, ‘RS’), with intrinsic trial-by-trial variability that can be described through stochastic Bayesian modelling (Orban de Xivry et al., 2013). Saccade trigger during pursuit is highly dynamic and contingent on both retinal position error (‘PE’) and RS. A related measure, the eye crossing time (which depends on PE and RS) has been shown to determine average saccade occurrence but fails to explain exactly when an actual saccade will be triggered (de Brouwer et al., 2002a). Here we model the computational strategy underlying the decision mechanism to trigger catch-up saccades during smooth pursuit initiation and maintenance in a closed-loop stochastic simulation within a Bayesian framework. In this model, sensory inputs (PE and RS, arising from the relative motion between the target and the eye) are delayed, corrupted by signal-dependent noise, and are independently estimated through Kalman filtering. Each Kalman filter computes a Bayes optimal probabilistic estimate of its respective sensory signal, i.e.: a mean value and its associated uncertainty. In line with observations that saccade

amplitude accounts for RS during pursuit (de Brouwer et al., 2002b), our model utilizes estimated RS to extrapolate the current estimated PE into the future, compensating for sensory and motor delays. In our model, a saccade is triggered if it can be determined with certainty (in a statistical sense) that the future PE will be outside an allowable PE range (ie: foveal image positions). In agreement with the decision-making literature, the decision signal is accumulated through leaky integration and triggers saccades upon crossing a fixed threshold of certainty. The model reproduces the distributions of saccade occurrence observed in humans across a range of step-ramp target motions during pursuit initiation and maintenance. This provides a general framework for the predictive trigger of saccades during smooth pursuit constrained by noisy, delayed, and dynamically varying sensory and motor signals.

Disclosures: **J. Coutinho:** None. **P. Lefèvre:** None. **G. Blohm:** None.

Poster

059. Eye Movements: Smooth Pursuit

Location: Halls A-C

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Program#/Poster#: 059.07/CC20

Topic: E.01. Eye Movements

Support: Gift from HHMI

F30-EY027684

Title: Updating of a Bayesian-like prior for visual motion speed in the smooth eye movement region of the frontal eye fields

Authors: *T. DARLINGTON, S. G. LISBERGER
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Abstract: Nearly all sensory-motor behaviors are guided by a complex interaction between expectation based on past experience and sensory information. This interaction has been modeled well by the Bayesian framework in which expectation is the “prior”, sensory information is the “likelihood”, and the interaction of the two derives the “posterior”. Given the dynamic nature of the world in which we live, the usefulness of priors may depend in part on their adaptability. While the Bayesian framework seems to explain behavior quite well, our goal is to understand how the operation of neural circuits give rise to adaptive Bayesian-like behavior. Previous work has shown that the smooth pursuit eye movement system utilizes an adaptable Bayesian prior for visual motion speed, that this Bayesian prior could be implemented by controlling the gain of visual-motor transmission, and that the smooth eye movement region of the frontal eye fields (FEF_{SEM}) plays a major role in visual-motor gain control. Therefore, we recorded single units in the FEF_{SEM} of rhesus macaques while they pursued moving visual

targets. To manipulate the expectation of the monkey, we controlled the statistics of target speeds that the monkey experienced. During a fast context, 80% versus 20% of the trials presented target speeds of 20 versus10 deg/s. During a slow context, 80% versus 20% of the trials presented target speeds at 2 versus 10 deg/s. To manipulate the strength of sensory evidence, we presented targets of high- (strong visual motion) and low-contrast (weak visual motion). The eye speed in response to the 10 deg/s target motion is faster in the fast context and slower in the slow context. FEF_{SEM} preparatory activity tracks the statistics of target speeds and therefore encodes the prior. The time course and magnitude of the adaptation of preparatory neural activity and eye speed align quite well. Finally, adaptation of the prior can be accounted for fully by a model that uses FEF_{SEM} pursuit-related firing rate responses for updating. We conclude that Bayesian-like behavior is accomplished in the smooth pursuit eye movement system by co-opting neural mechanisms in place for a different purpose, the control of visual-motor gain.

Disclosures: T. Darlington: None. **S.G. Lisberger:** None.

Poster

059. Eye Movements: Smooth Pursuit

Location: Halls A-C

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Program#/Poster#: 059.08/CC21

Topic: E.01. Eye Movements

Support: NS092623

Title: Time course of multiple components of directional motor learning in smooth pursuit eye movements

Authors: *N. J. HALL[1], S. G. LISBERGER[2]
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Abstract: We investigated the components of motor learning and the timescales over which they take place to characterize behavioral correlates of multiple neural components of cerebellar motor learning. We studied motor learning as monkeys performed smooth pursuit eye movements during a direction-change task. In each learning trial, a target begins to move in an initial pursuit direction and the animal follows it with his eyes. After a short fixed interval or 250 ms, the moving target suddenly, but predictably, changes direction. Over multiple presentations of the learning trials, pursuit begins to anticipate the direction change (Medina et al., 2005) by showing a modification of eye velocity just before the target changes direction. By measuring the magnitude of this predictive velocity change we are able to quantify motor learning.
Here we asked how 3 different components of motor learning develop across long timescales. Previous work has shown that learned behavioral responses are present after single trials and grow over the course of 100 trials (Yang and Lisberger, 2010; Yang and Lisberger, 2013). We

analyzed learned eye velocity over 1000 repetitions of the direction-learning task. We found that the increase in learning observed over multiple trials consists of at least 2 components: an early component that rises and saturates quickly over the course of tens of trials; and a late component that grows slowly over the course of hundreds of trials. We further explored the effect of single trial learning on these 2 components by manipulating the inter-trial interval (ITI). ITI usually was 2.5 seconds to allow for single trial learning. We probed for and identified learning components in the absence of single trial learning by contriving long ITI trials of 6 seconds at strategic times during the progression of learning. We chose an ITI of 6 seconds because this is long enough for single trial learning to disappear. Thus, consolidated components of motor learning are expressed alone, without any expression of single trial learning, after a 6 second ITI. Our results suggest that the 2 distinct components of pursuit motor learning that grow over multiple trials comprise consolidated learning, and that the single-trial learning component interacts multiplicatively with consolidated motor learning over long timescales.

Disclosures: **N.J. Hall:** None. **S.G. Lisberger:** None.

Poster

059. Eye Movements: Smooth Pursuit

Location: Halls A-C

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Topic: D.09. Visual Sensory-motor Processing

Support: NIH Grant EY03878

IBS-R015-D1

Title: Neural latency co-variation in primate frontal cortex predicts correlations with variation of behavioral reaction time

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Abstract: Variation of neuronal activity is an important feature of the activity of populations of neurons for representing sensory and motor events. Pooling across large populations of neurons can eliminate variation that is independent among neurons, but correlated variation propagates through sensory-motor circuits and contributes to the observed variation in motor behavior. Because of correlated variation, the activity of individual neurons can predict a significant fraction of the variation of motor behavior. We have previously shown that this account holds true for the amplitude and latency of neural responses in area MT, and that the correlation of a

single neuron with behavioral variation depends on its synchronization with the rest of the neural population.
Now, we show that the same account holds for the relationship between the latency of responses in the smooth eye movement region of the frontal eye field (FEFsem) and the latency of the initiation of pursuit eye movements. We recorded from multiple single neurons in the FEFsem of two rhesus monkeys while they performed a smooth pursuit eye movement task. We observed that the neural latency co-varies on a trial-by-trial basis with behavioral latency when a single neuron is in a correlated population, as indicated by synchronization of spiking with a LFP wavelet in the 5-15 Hz frequency range. The strength of synchronization between the neuron and the population varies across trials, and determines how well the strength of the single neural latency variation is correlated with the behavioral latency variation. These results suggest that FEFsem makes an important contribution to behavioral latency, and the presence of trial-by-trial correlations between neural and behavioral latency implies that little or no latency variation is added downstream.

Disclosures: **J. Lee:** None. **S.G. Lisberger:** None.

Poster

059. Eye Movements: Smooth Pursuit

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Topic: E.01. Eye Movements

Support: NIH Grant EY021286

Title: Illusory motion reveals smooth pursuit of large objects is driven by motion, not position

Authors: *S. J. HEINEN[1], S. N. WATAMANIUK[2], Z. MA[1]
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Abstract: Pursuit of small stimuli is driven by retinal motion, but also by position correction, which results in the stimulus being foveated. We have shown that pursuit of large objects is driven by retinal motion that is spatially integrated. Although foveation of a large object is not possible if it subtends a visual angle greater than the fovea, the pursuit system could still compute its center of mass and correct for position error. Here, we employ an illusory motion stimulus to show that the pursuit system does not follow the centroid of a large object, but rather is driven by integrated motion information. The target consisted of four Gabor patches, each drifting within a circular aperture and arranged as a diamond shape. It is known when an aperture containing a single Gabor translates in the same direction that the Gabor drifts, it is perceived to move faster than it does. In the current experiment, observers pursued the diamond as it

translated leftward or rightward at 10°/s. Gabor drift directions were the Same, Opposite, or Orthogonal to the translation direction. Pursuit gain was higher in the Same than in the Opposite condition, evidence that the pursuit system integrated the local drifting motion patches along with the translating motion. However, "catch-up" saccades reversed the gain changes invoked by the drifts. To test if the effect originated in motion perception, we measured the perceived speed of the translating stimulus using a staircase method. Consistent with pursuit, global perceived speed was higher in the Same than in the Opposite condition. We further asked if drift integration is cancelled when a non-illusory local motion cue is provided, by surrounding each Gabor patch with a frame. The frames reduced the difference between the Same and Opposite conditions for both pursuit and perception. The results suggest that when pursuing large stimuli, the pursuit system integrates motion, regardless of whether eye position deviates from the center of mass. However, the saccadic system is sensitive to position deviation from the centroid, and attempts to correct it.

Disclosures: S.J. Heinen: None. **S.N. Watamaniuk:** None. **Z. Ma:** None.

Poster

059. Eye Movements: Smooth Pursuit

Location: Halls A-C

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Program#/Poster#: 059.11/CC24

Topic: E.01. Eye Movements

Title: Perceived location of a pre-pursuit target when pursuit movement direction is predictable versus unpredictable and the target location varies

Authors: *J. POLA, H. J. WYATT
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Abstract: When we make smooth pursuit eye movements to follow a moving target, the background visual field is perceived as stable even though the retinal image of the field moves across the retina. One explanation for this stability is that a pursuit extraretinal signal (e.g., a corollary discharge) causes a shift of perceived location relative to retinal locus which cancels the perception of background displacement. In some recent work we explored the overall features of the shift (Pola & Wyatt, 2016): Subjects pursued a target moving in the same direction across trials and reported on the perceived location of a test-flash with respect to a pre-pursuit target (presented briefly before pursuit) at the initial fixation position. The results show a shift of perceived location that began before the pursuit, occurred more slowly than the pursuit, and had final amplitude less than that of the pursuit. These findings raise some important questions: are the features of the shift a consequence of pursuit movement occurring predictably in one direction and/or the pre-pursuit target being at the fixation position? Given these issues, the present study used three conditions: 1) pursuit occurring in one direction over trials, either to

the right or left; 2) pursuit occurring randomly to the right and left over trials; and 3) pursuit with different pre-pursuit target locations. In each of these conditions, the subject reported on the perceived location of a test-flash (10 ms) presented at different times before, during or after pursuit (at 15 deg/sec) relative to the pre-pursuit target (viewed and extinguished before pursuit). By varying test-flash location we were able at each time to find the target point of subjective equality (TPSE), i.e., a test-flash perceived to be at the pre-pursuit target location. The difference between eye position and TPSE (EP - TPSE) provides a measure of the shift of perceived location relative to retinal locus. Based on this, a main finding is that the shift of perceived location was not affected by pursuit directional biases or pre-pursuit target location. That is, in all three conditions the shift began shortly before pursuit onset, occurred more slowly than the ongoing pursuit, and ended up with amplitude that was smaller than that of the overall pursuit. Thus, the dynamics of the pursuit-perception system are invariant over a variety of stimulus situations.

Disclosures: J. Pola: None. **H.J. Wyatt:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.01/CC25

Topic: E.01. Eye Movements

Support: DFG LA 952-6

Title: Primary but not secondary visual rewards influence saccade adaptation

Authors: A. MEERMEIER[1], S. E. GREMMLER[2], K. RICHERT[2], *M. LAPPE[2]
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Abstract: Saccadic adaptation is an oculomotor learning process that maintains the accuracy of eye movements to ensure effective perception of the environment. It is studied by shifting the saccade target mid-flight, thereby introducing a post-saccadic error and prompting a change in saccade amplitude. Although saccadic adaptation is commonly considered an automatic and low-level motor calibration in the cerebellum we recently found that strength of adaptation is influenced by the visual content of the target: pictures of humans produced stronger adaptation than noise stimuli. This suggests that meaningful images may be considered rewarding or valuable in oculomotor learning. Wanting to establish the boundaries of this effect, we ran 3 experiments. In the first we tested whether cognitive (literate) meaning could induce the same effect by comparing targets consisting of words and non-words. The results of twenty subjects revealed no difference in adaptation strength (BF_{01}=2.96) In the second experiment we tested

whether stimuli that were associated with high and low value following long term self administrated reinforcement learning could induce the described effect. Twenty-eight expert gamers participated in two sessions of adaptation to game-related high and low value stimuli, but revealed no difference in saccadic adaptation (BF_{01}=5.7). Finally we replicated our finding of the influence of image content in reactive saccades. Twenty-two subjects adapted significantly more towards images of human figures in comparison to noise (p<.001).We conclude that saccadic adaptation is influenced by the primary value of the target image (human vs noise), but not by secondarily acquired value (words vs non-words, secondary reinforcers). Clear vision of a target is the product of a successful saccade. It is thought to have reinforcing qualities that organize saccade accuracy. The impact of human target images onto oculomotor learning might imply a specific value of clearly viewing evolutionary relevant images. Furthermore the interaction of target content with basic processes of oculomotor learning advocates a top down influence to a supposedly automatic calibration, possibly mediated via dopaminergic processing in the basal ganglia.

Disclosures: **A. Meermeier:** None. **S.E. Gremmler:** None. **K. Richert:** None. **M. Lappe:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: E.01. Eye Movements

Support: The study has been funded by the Russian Academic Excellence Project '5-100'.

Title: Saccadic reactions and visual ERP potentials at the experimental scheme with distracters under stimulation of dominant and subdominant eye

Authors: *V. MOISEEVA[1,2], M. SLAVUTSKAYA[2], N. FONSOVA[1,2], V. SHULGOVSKIY[2]
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Abstract: For successful goal-directed behavior, it’s crucial to attend relevant stimuli in the visual field while ignoring distractor elements. The oculomotor system is a good model for the study of this competition between different elements. The goal of this research was to analyse spatial-temporal parameters of saccades and presaccadic EEG-potentials at the simultaneous presentation of the target and distracting stimuli to the leading and unleading eye. The complex of the positive and negative potentials was revealed in the saccade latent period. Latency of all components was shorter upon presentation of stimuli to the left, unleading eye, that may indicate the earlier saccade preparation. At the same time LP saccades were longer in this conditions (p<0.05). The results show that early potentials N1 and P1 were higher in amplitude and

dominated in the controlateral parietal-occipital areas. It can be reflection of visual sensory processing. The amplitude of the later negative potential N2 at the stimulation of the right eye increased in the case when target stimulus was at the same location than at the previous realization. It's possible that N2 component is connected with processes of preliminary extracting of motor program from memory together with attention processes. N2 amplitude was higher when the distance between target and distracting stimuli was 15 degrees in comparison with the minimal distance 5 degrees. It's corresponded with LP data. The findings show an active role of attention and decision-making processes in saccade programming.

Disclosures: V. Moiseeva: None. **M. Slavutskaya:** None. **N. Fonsova:** None. **V. Shulgovskiy:** None.

Poster

060. Eye Movements: Saccades

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Topic: E.01. Eye Movements

Support: NIH Grant NS078311

Title: Modulation of error-sensitivity during sensorimotor learning

Authors: *E. SEDAGHAT NEJAD, R. SHADMEHR
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Abstract: A number of studies have recently examined the effect of positive and negative motivational feedbacks, reward and punishment, on motor learning. Here, we assessed another two motivational factors -- the intrinsic value of the visual stimulus (Face/Noise) and task demand (Informative/Null). In both cases, we used a gain-down saccade-adaptation task design during which the cue-target was shown 15 degrees (either to the right or left) away from the start-target and after detection of primary saccade the end-target was shown 5 degrees backward in the 10 degrees relative location. In the first paradigm, we used the human faces and meaningless visual noises as high-value and low-value visual stimuli. We conducted both visually-guided and memory-guided types of this paradigm and in both cases, the results showed that despite the shorter reaction times toward faces, the rate and extent of adaptation was not significantly different between high-value and low-value stimuli. We concluded from these results that the stimulus-value alone cannot modulate error-sensitivity. As an alternate hypothesis, we considered the possibility that instead of the value of the stimulus that drives the movement, value of the error that results from the movement may be the critical factor in modulation learning from error. To address this hypothesis, we conducted a second paradigm using task demand as a factor which influences error-value. Each trial of the second paradigm

consists of two stages -- information-acquisition and decision-making. During information-acquisition stage, participants made saccades toward either an informative stimulus which represents number 1, 2, 3, or 4 in the form of black dots or a null stimulus which is a visual noise and represents no information. During decision-making stage, they chose a number either based on the number of black dots in the informative stimulus or an arbitrary choice in the case of null stimulus. We found that the demand for information-acquisition resulted in faster learning rates and shorter reaction times toward informative stimulus. Furthermore, the results of the state-space analysis showed higher error-sensitivity in that case. Together, these results indicated the dissociable effect of stimulus-value and error-value on motor learning and highlighted potential functional connections between reinforcement and error-based learning mechanisms of the brain.

Disclosures: **E. Sedaghat Nejad:** None. **R. Shadmehr:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

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Topic: E.01. Eye Movements

Support: NIH Grant 4R01NS078311-05

Title: Evidence of slow and fast learning processes in early and late halves respectively of saccades during cross-axis saccade adaptation

Authors: *S. P. OROZCO[1], D. J. HERZFELD[2], R. SHADMEHR[3]
[1]Biomed. Engin., [2]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [3]Dept Biomed. Eng, Johns Hopkins Univ. Dept. of Biomed. Engin., Baltimore, MD

Abstract: One useful model of motor adaptation is the two-state learning model in which there are two parallel learning processes, one that learns quickly but forgets quickly (fast process) and one that learns slowly but also forgets slowly (slow process). Here, we show evidence of the fast and slow processes in the late and early part of the same saccade.
We hypothesized that changes to the later part of the saccade would behave like the fast process, whereas changes in the early part of the movement would proceed like the slow process. To test this idea, we designed a cross axis saccade adaptation paradigm in which the primary saccade direction was vertical but the target jump was horizontal. This was to be able to differentiate between the primary movement signal and the adaptation signal since they were in orthogonal directions.
Subjects (n = 35) adapted to approximately 1.0 degrees of the 5-degree perturbation. In order to test adaptation in the early and late parts of the saccade, we divided each saccade into early and late phases based on peak speed. For each saccade during the adaptation period, we subtracted

the mean baseline (prior to perturbation onset) saccade velocity profile to isolate the velocity due to adaptation. We then integrated the early and late phases of the horizontal velocity profile. Both integrals increased as a function of trial number, but the integral after peak speed increased more quickly and reached a higher asymptote. In addition, only the adaptation in the late half of the movement showed forgetting during the set breaks. We quantified this time effect by binning the movements during the adaptation period based on inter-trial interval (ITI). Late adaptation showed a strong decay as a function of increased ITI, whereas early adaptation remained almost completely stable. In contrast, binning the movements by error size showed a positive relationship between increased error size and trial-to- trial change in horizontal displacement during both phases of the movement.
Finally, based on previous work in our lab suggesting savings may be due to an increase in error sensitivity of the fast process, we hypothesized that a second exposure to the perturbation following washout would differentially increase adaptation in the later half of the movement. We conducted a savings experiment (n = 18) to test this secondary hypothesis. Only the late part of the movement exhibited savings; adaptation reached asymptote much more quickly during the 2nd exposure than during the 1st exposure, whereas there was no difference between 1st and 2nd exposure in the early part of the movement.

Disclosures: S.P. Orozco: None. **D.J. Herzfeld:** None. **R. Shadmehr:** None.

Poster

060. Eye Movements: Saccades

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Topic: E.01. Eye Movements

Support: SUNY Brain Network of Excellence Award

Title: Activity of visually-responsive superior colliculus neurons in a visual search task using naturalistic object categories

Authors: *B. M. COOPER[1], H. ADELI[2], G. ZELINSKY[3], R. MCPEEK[1]
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Abstract: In real-world visual search tasks, the goal is often to locate an object of a particular category (e.g., a pencil) rather than a specific object exemplar (e.g., a short red pencil). However, neurophysiological studies of saccade target selection in the superior colliculus (SC) generally rely on tasks in which the target is defined by a single feature or a combination of simple features. Previously (SfN 2016), we presented behavioral evidence that macaques are able to successfully use learned categorical target templates to guide search in a visual search task using

naturalistic target and distractor object images. We also found that the fixation locations selected by macaques fit well with the predictions of an image-based model of attention in the SC, MASC (Adeli et al. 2017), that incorporates constraints based on the known anatomy and physiology of the primate SC. Here, we investigated SC activity during saccade target selection in a similar visual search task. Macaques were trained to search and fixate targets from two specific object categories (teddy bears and butterflies), which were presented with distractors consisting of images of other random category types. In this task, eye movement behavior was unconstrained, and on 50% of trials the target was absent. The array geometry was evenly spaced about fixation and oriented such that one of the task objects was always centered in the neurons response field. We recorded activity of visually-responsive neurons in the intermediate layers of the SC during the task. We found that, in many cells, visual responses were largest when an image belonging to the target category was presented in the cell's response field, even when the upcoming saccade was directed elsewhere. MASC also provided predictions of the relative priority of the distractor objects, based on their bottom-up salience and their similarity to the target category. We found that the distractors that were assigned a low priority by MASC produced less visual activity than distractors that were assigned a high priority. These observations provide further validation of the model, MASC, and are consistent with the idea that visual responses in the SC comprise a priority map not only in simplified feature search tasks, but also when macaques perform a gaze-unconstrained visual search task using complex, naturalistic images.

Disclosures: B.M. Cooper: None. **H. Adeli:** None. **G. Zelinsky:** None. **R. McPeek:** None.

Poster

060. Eye Movements: Saccades

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European Research Council

Title: Cerebellar control of saccades by the size of the active population in the caudal fastigial nucleus

Authors: *L. GOFFART[1], J. QUINET[2], C. BOURRELLY[2]
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Abstract: The caudal fastigial nucleus (CFN) is critical for generating accurate saccades toward a visual target. Its pharmacological inactivation alters the amplitude of their horizontal component: it is hypermetric for ipsilesional saccades and hypometric for contralesional ones. A recent study reported that "ipsilesional saccades showed more endpoint variability than did normal saccades" and that the "inactivation effects on saccade noise are explained by a decrease of the feedback gain and an increase of planning and/or signal dependent motor noise" (Eggert et al., 2016). In the framework of a control of saccade amplitude by negative feedback, the hypermetria of the horizontal component of ipsilesional saccades can indeed be explained by an underestimation of the current eye displacement. However, instead of adding a notion which is rather neurophysiologically undetermined (“noise”), we propose that the endpoint variability actually reflects the size of the active population in the CFN. This conjecture derives from the results of Quinet & Goffart (2015) who showed that the size of saccades evoked by electrical microstimulation in the fastigial nucleus increases with larger current. According to this hypothesis, if an injection of muscimol is made not exactly centered in the fastigial oculomotor region, the number of saccade-related neurons which are inactivated by the pharmacological agent should increase as it diffuses, resulting in a time-varying dysmetria. Moreover, this effect of diffusion should not be restricted to the generation of ipsilesional saccades, but should concern also the generation of contralesional ones. We will show examples of inactivation experiments performed in head-restrained monkeys where the magnitude of dysmetria did not change with time and others where it increased. Depending upon the experiment, this time-varying effect affected either ipsilesional or contralesional saccades. Thus, the so-called “noise” inferred from the variability of endpoints after CFN inactivation seems to result from an increase of the number of neurons which are silenced by the pharmacological agent (muscimol). The possibility to independently alter the horizontal component of ipsilesional or contralesional saccades suggests independent output channels from the CFN to the saccade-related premotor neurons. More fundamentally, these observations point to the fact that the size of the population of active neurons in the CFN plays a major role in the cerebellar control of the horizontal amplitude of saccades : it participates to their dynamics by recruiting the appropriate number of premotor burst neurons, excitatory and inhibitory.

Disclosures: **L. Goffart:** None. **J. Quinet:** None. **C. Bourrelly:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.07/CC31

Topic: E.01. Eye Movements

Title: Correlations between control of saccadic eye movements and performance in other cognitive tasks in younger adults, older adults and patients with Parkinson’s disease

Authors: *J. OUERFELLI-ÉTHIER[1], B. ELSAEID[2], J. DESGROSEILLIERS[4], D. P. MUNOZ[2], G. BLOHM[3], A. Z. KHAN[1]
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Abstract: Cognitive control is defined as the ability to act flexibly in the environment by either behaving automatically or inhibiting automatic behaviour and can be measured using an interleaved pro/anti-saccade task. Decline in cognitive control has been attributed to normal aging and neurological illnesses such as Parkinson's disease (PD) in parallel with other cognitive abilities, highlighting its role played in information processing and working memory. However, little is known about the relationship between cognitive control and other cognitive processes such as visual memory, decision making, and visual search. Here, we correlated the incidence of impaired cognitive control with deficits in visual memory, decision making, and visual search in three groups of participants: younger adults (M = 22.75, SD = 3.8; n = 34), older adults (M = 64.76, SD = 7.4; n = 21), and patients with idiopathic PD (M = 70.94, SD = 8.2; n = 16). Participants performed four tasks: interleaved pro/anti-saccade, visual memory, decision making and visual search (both serial and pop-out). Results show that within each group, anti-saccade error rate and reaction times of correct anti-saccades were significantly correlated with visual memory error rate. Correct decision making times were significantly correlated with anti-saccade error rate and reaction times only in older adults and PD patients. For visual search, PD patients showed a significant relationship between reaction times for correct pro-saccades and search times (both pop-out and serial). These results support the hypothesis of excessive reliance of bottom-up processes in PD to compensate for reduced top-down control. For younger adults, there was a significant correlation between serial search performance and both anti-saccade error rate and correct pro-saccade reaction times. In older adults, this relationship was absent but anti-saccade error rate significantly correlated with pop-out search times. In summary, we found significant relationships between cognitive tasks and cognitive control as measured through the interleaved pro/anti-saccade task across and within participant groups, providing evidence of the appropriateness of the use of the interleaved pro/anti-saccade task as a measure of overall cognitive control.

Disclosures: J. Ouerfelli-Éthier: None. **B. Elsaeid:** None. **J. DesGroseilliers:** None. **D.P. Munoz:** None. **G. Blohm:** None. **A.Z. Khan:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.08/CC32

Topic: E.01. Eye Movements

Support: DFG

Title: Memory-guided microsaccades: Behavior and physiology

Authors: *K. F. WILLEKE[1], X. TIAN[1], J. BELLET[1], A. RAMÍREZ-CÁRDENAS[2], Z. M. HAFED[1]
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Abstract: Microsaccades are commonly described as “involuntary”. However, under a variety of task conditions, microsaccade directions, amplitudes, and frequencies can be systematically modulated. While these results hint at voluntary control, they are primarily derived from likelihood measures rather than “at will” triggering of individual movements, and the overwhelming description of these movements in the literature remains to be that they are “involuntary”. Here we asked whether individual movements in the microsaccade amplitude range can be triggered: (1) “on demand” based on an arbitrary instruction, (2) without special training, (3) without visual guidance, and (4) in a spatially- and temporally-accurate manner. Two macaque monkeys and 7 human subjects performed a memory-guided saccade task. In this task, an eccentric flash was presented briefly (~50 ms). Subjects maintained flash location in memory for ~300-1100 ms, after which the fixation spot disappeared, providing a “go” command to generate a saccade to the remembered location. After an additional grace period, the remembered stimulus re-appeared allowing subjects to visually correct any remaining errors. The monkeys were only trained on the task with saccades >3 deg in amplitude, and humans were only given verbal instructions and minimal training. We then collected data from trials of random target eccentricities (0.1-16 deg) and directions (0-360 deg). All subjects naturally generated memory-guided movements even less than 0.5 deg in amplitude. These movements were highly directionally accurate, and while their amplitudes may have been quantitatively less accurate than visually-guided corrections (primarily overshooting in the memory condition), dependence of landing error on eccentricity was not qualitatively different between the memory and visually-corrective movements. Importantly, we ran the human subjects on 2 control versions of the task with manual pointing, and similar overshooting for foveal targets was observed. We then recorded neural activity from the superior colliculus (SC) of one monkey using linear electrode arrays placed in the rostral region. We analyzed multi-unit activity and observed similar movement-related discharge for “memory-guided microsaccades” and visually-guided movements of similar amplitudes. We conclude that microsaccades can be generated voluntarily, and that any spatial inaccuracies in memory-guided microsaccades are likely not due to an inability of the oculomotor system to voluntarily trigger a tiny saccade. We also conclude that microsaccade-related discharge in the SC can occur in the absence of visual stimulation by a movement target.

Disclosures: K.F. Willeke: None. **X. Tian:** None. **J. Bellet:** None. **A. Ramírez-Cárdenas:** None. **Z.M. Hafed:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.09/CC33

Topic: E.01. Eye Movements

Support: NSERC Discovery Grant

NSERC CGS-M

OGS

Title: Modulation effects and time course of target-distractor similarity on saccade curvatures

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Abstract: According to the weighted average account, saccade curvatures are due to interactions between competing saccade vector representations in the oculomotor system. Given that the task relevance of visual stimuli is encoded in oculomotor neural substrates (Fecteau & Munoz, 2006), a prediction of the weighted average account is that saccade curvatures are functionally related to the level of cognitive activation/inhibition elicited by distractors. To examine this potential relationship, we created stimuli by conjoining individual line segments into holistic objects whereby the similarity between stimuli was manipulated by varying the number of individual line segments shared between stimuli. The relative similarity between two bilateral distractors and a target was systematically varied on a search task in which participants (N = 24) saccaded to the target. When distractors were equally similar, saccades deviations were not different from baseline, Z = -0.26, p = 0.798; Z = -0.15, p = 0.882. When one distractor was more similar, saccades curved away from it, Z = -3.11, p = 0.002; Z = -2.65, p = 0.008, and this shift occurred during the first 60-80% of the length of the saccade, which corresponded to the first 23-31 ms. Saccade curvatures were also linearly related to relative similarity, $F(1,2) = 32.64$, p = 0.029, R^2 = 0.94; $F(1,2) = 44.92$, p = 0.022, R^2 = 0.96. As saccade trajectories were systematically biased away from the stimulus with higher target-similarity in a pair of spatially balanced stimuli, the current results suggested that a vector weighted-average computation performed prior to saccade initiation determined the final movement trajectory, consistent with neurophysiological models of vector encoding in critical oculomotor substrates. Critically, as computing target-similarity required a detailed analysis of shared features between objects, these results suggested that high-level object representations with associated features modulate the vector weights encoded by the oculomotor system.

Disclosures: **D.H. Kehoe:** None. **M. Fallah:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.10/DD1

Topic: D.09. Visual Sensory-motor Processing

Support: CIHR

Title: Comparison of visual-motor transformations of unit activity between the frontal eye fields and supplementary eye fields during head-unrestrained gaze shifts

Authors: *V. BHARMAURIA[1], A. SAJAD[2], H. ARORA[1], X. YAN[1], H. WANG[1], J. D. CRAWFORD[1]
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Abstract: The neural underpinnings of visual-motor transformations during naturally coordinated behaviors are poorly understood. We investigated the visual-motor transformations for gaze by discriminating the spatial codes embedded in the visual (V) and motor (M) responses of simultaneously recorded single-unit and multi-unit activities of the frontal eye fields (FEF) and supplementary eye fields (SEF) in two head unrestrained monkeys. Monkeys made centrifugal gaze shifts toward the remembered location of briefly presented targets. Targets were distributed pseudo-randomly across receptive fields of neurons to allow data recording from a wide range of spatial configuration. Target presentation was followed by a variable delay and then a go signal. Animals were also provided with an allocentric cue (a large cross) in the vicinity of the target, which either remained stationary or shifted in during the memory delay period. Animals were provided with relatively large reward windows (10-14°) to allow gaze errors, and were otherwise allowed to choose their own eye-head coordination strategy. Our preliminary analysis has focused on egocentric coding, employing a spatial model-fitting method used previously (Sajad et al. Cer. Cortex 2015; Eneuro 2016). Single-unit analysis confirmed that the FEF visual burst (n=17) is spatially selective and encodes the target in eye-centered coordinates (Te), whereas the motor activity (n=14) encodes gaze relative to initial eye orientation (Ge). Analysis of multiunit FEF activity gave similar results for the V (n=9) and M (n=5) responses, suggesting that spatial codes are clustered within the FEF. In contrast, during the same recordings, SEF neurons were broadly tuned and showed no significant preference for any egocentric model, with only slight trends toward Te or Ts (Target-in-space) in their visual responses. A behavioral analysis has shown that the allocentric cue also influences gaze endpoints (Li et al. J. Vision 2017), but allocentric models have not yet been incorporated into our unit-recording analysis. Further analysis will focus on testing allocentric models, gain fields,

spatial transformations during memory delay, and synchrony of single- and multi-unit activity between the FEF and SEF.

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Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.11/DD2

Topic: E.01. Eye Movements

Support: Rachel C. Atkinson Fellowship

Title: Brain response components elicited by saccadic eye movements across natural images of faces

Authors: *Y. JIA, C. W. TYLER
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Abstract: Introduction. In most previous electroencephalography (EEG) experiments, visual processing is examined with large eye movements precluded, making it difficult to determine the cortical mechanisms involved in the control of eye movements. A previous study (Jia & Tyler, 2016) validated the capability of simultaneous EEG and eye movement measurements with electrooculography (EOG) signals. The current study co-registered the EEG and EOG signals to reveal neural correlates of natural image processing while making fixational eye movements across images of faces.
Methods. Fixation targets consisting of 18 white circles appeared in random order in a window (29° by 22°) filled with a) a blank field, b) a white noise pattern, c) a natural image of a face, or d) only the facial features within the circles with a noise pattern elsewhere. Participants were required to saccade onto each stimulus as it was presented. EEG and EOG were measured simultaneously with a high-density EGI electrode net at a 500 Hz sampling rate. The resultant EEG signals were pre-processed to remove blinks and other artifacts and analyzed by a) the standard approach of averaging across preselected electrode positions and b) Principal Components Analysis (PCA) to reveal spatiotemporal saccade-related and cortical visual fixation- potentials.
Results. The averaging approach showed only a transient response around the time of the saccade. The PCA analysis revealed a primary EOG eye movement component with a saccade-like waveform deriving from the forehead region. Two forms of slow anticipatory component preceding the saccades had prefrontal localization. The saccades were accompanied by a transient Frontal Eye Field component. A perisaccadic posterior component was interpretable as

representing the neural substrate for saccadic suppression. Occipital components peaking 100-200 ms after the saccade were interpretable as the cortical responses to the face targets, and were absent for the blank field condition. The components obtained for each individual participant were generally consistent with those from the group average.
Conclusion. These findings show that spatiotemporal PCA can identify a range of saccadic control and visual cortical response components during saccadic exploration of facial images.
Reference. Jia, Y. & Tyler, C.W. The value of simultaneous EOG and EEG recording for measurement of saccade-related brain activity. Program No. 55.09. 2016 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2016. Online.

Disclosures: Y. Jia: None. **C.W. Tyler:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.12/DD3

Topic: E.01. Eye Movements

Support: NIH Grant EY021286

Title: Foveation engages the saccadic system with or without a stimulus

Authors: *S. N. WATAMANIUK[1,2], J. BADLER[2], S. J. HEINEN[2]
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Abstract: Previously we showed that fixation stimuli lacking a central element produced fewer microsaccades than those with a central element. We reasoned that this was because the central element triggered attention, which caused the saccadic system to foveate it. To test this, we had observers fixate a 9-dot stimulus consisting of a 6° circular array of eight dots, and a central one. In separate blocks of trials, they had to detect random luminance increases at either the central dot, or at one of the peripheral dots randomly chosen. Eye movements were measured using an EyeLink 1000 eye tracker. We found that saccade rate was higher when the task was on the central spot than when it was on the peripheral ones, supporting the idea that attention at the central spot was evoking saccades. We then asked if the stimulus was necessary to activate the saccadic system, or if foveally-directed attention alone was sufficient. In the second experiment, observers fixated only the 8-dot peripheral array with no central element. In one condition, the attention task was on the peripheral dots as before. In the other condition, the detection task was on a threshold stimulus occasionally flashed in the center. We found that saccade rate was higher when observers attended to the center despite that no stimulus was present. Thus, even foveating an imaginary stimulus engaged the saccadic system. The results suggest that endogenous

attention directed to the fovea can engage the saccadic system and that physical position error is not necessary for the generation of “corrective” microsaccades.

Disclosures: S.N. Watamaniuk: None. **J. Badler:** None. **S.J. Heinen:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

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Program#/Poster#: 060.13/DD4

Topic: E.01. Eye Movements

Support: FAPEMIG (grant no. APQ- 00299- 13)

FAPESP Research, Innovation and Dissemination Center for Neuromathematics (grant no. 2013/07699-0, S. Paulo Research Foundation)

CAPES

Title: Main sequence characteristics of 3D head saccades in owls

Authors: *M. D. BORGES[1], D. DUARTE[2], C. AMARAL[3], J. BARON[3]
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Abstract: Because of the highly restricted mobility of their eyes, owls reallocate their visual gaze essentially by making rapid head movements of saccadic nature. This work intends to provide a detailed 3D-kinematic analysis of such movements. More specifically, we seek to determine whether the latter are as predictable as primate eye saccades due to stereotyped relationships between saccade peak velocity, duration and amplitude, a feature also known as “main sequence”. Data were collected from 4 burrowing owls (Athene cunicularia) let to inspect freely a richly structured indoor environment from a low-height perch. Head position and orientation (pose) were recorded in 3D space using a commercial high-resolution electromagnetic tracking device (3D Guidance trakSTAR™ system). Dual quaternion were used to analyze pose data. This algebraic structure provides an unified, compact, and geometrically explicit form of representing the translation and rotation of a rigid body, which does not suffer from classical 3D representation problems, such as loss of degrees of freedom or rotational singularities. The resulting quantity derived from this transformation was the angular velocity about the instantaneous rotation axis of the head-in-space. Data were then smoothed using a nonlinear maximum a posteriori (MAP) state-path estimator, whereby velocity values were modeled by stochastic differential equations embedded within Wiener processes. Finally, saccades were automatically identified by a new algorithm developed by our group, which relies on velocity threshold and detection theory. The results reveal that the peak velocity, amplitude

and duration of burrowing owl's head-saccades are systematically related by a main sequence profile that is qualitatively similar to that described for saccadic eye movements in human and non-human primates. Model selection analysis showed that a power-law function is better suited to describe the main sequence for the entire range of saccade amplitudes. No significant amount of inter-subject variability of main sequence profiles was found. Interestingly, in-flight changes of rotation axis inclination were observed for about 40% of head saccades. This finding may indicate that head saccades are at least partially controlled by online closed-loop feedback mechanisms. Alternatively, it may be that the skeletomuscular head-neck plant receives motor control signals from independent neural circuits with variable delay lines.

Disclosures: **M.D. Borges:** None. **D. Duarte:** None. **C. Amaral:** None. **J. Baron:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.14/DD5

Topic: E.01. Eye Movements

Support: CIHR

Title: Task and layer specific responses during automatic and controlled saccades in marmoset prefrontal and posterior parietal cortex

Authors: *K. D. JOHNSTON[1], S. EVERLING[2]
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Abstract: Parietofrontal networks have long been established as a critical neural substrate for a variety of cognitive processes. Less well understood are the neural computations occurring across cortical layers both within and between these areas during these processes. This is, in part, due to the practical difficulty of performing laminar recordings in well-studied frontal and parietal areas of the rhesus macqaque, such as the frontal eye fields (FEF) and the lateral intraparietal area (LIP), as they lie deep within sulci. The common marmoset (Callithrix jacchus) is a New World primate that shows considerable promise as a model animal for neuroscience research, due in part to a largely lissencephalic cortex that allows laminar recordings using linear electrode arrays. Here, we investigated layer-specific contributions within frontal and parietal cortex to cognitive processes by carrying out simultaneous laminar recordings in prefrontal and posterior parietal cortex of the awake behaving marmoset during performance of a task that required them to saccade either toward or away from a highly salient visual stimulus in short blocks of trials. In this task, animals were required to first fixate a central instruction cue. Following this, circular stimuli were presented simultaneously to the left and right equidistant

from fixation. Of these stimuli, one was larger (.8 deg) and of higher luminance (10 cd/m2) than the other (.18 deg, 4 cd/m2). Animals were required to fixate either the more or less salient stimulus, dependent on the task instruction, to receive a liquid reward. On *automatic* trials, saccades to the more salient stimulus were rewarded, while on *controlled* trials this contingency was reversed. We observed layer-specific and task-selective responses in the local field potentials (LFP's) recorded in both areas. Specifically, we found task-selective beta-band activity, and more robust visual and saccade-related responses in the deeper layers of PFC and PPC. These data provide insights into the cortical microcircuitry of automatic and controlled saccades in the frontoparietal network of primates.

Disclosures: K.D. Johnston: None. **S. Everling:** None.

Poster

060. Eye Movements: Saccades

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.15/DD6

Topic: E.01. Eye Movements

Support: Korea NRF Grant 2015M3C7A1064833

Title: Modulation of human saccade behavior using low-intensity focused ultrasound

Authors: *H. KIM[1], K. PAHK[1], S.-H. YEO[2]
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Abstract: Low-intensity focused ultrasound (LIFU) has recently gained attention as a novel neuromodulation technique because of its superior spatial resolution and depth penetrability compared to conventional non-invasive neuromodulation modalities such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS). The region-specific neuromodulatory effects of LIFU have been demonstrated in various animal species (rodents, rabbits, sheep and monkeys) and humans via behavioural responses, functional neuroimaging data (fMRI, PET), electrophysiological measurements (motor- and visual-evoked potentials) and microdialysis techniques (neurotransmitters). In this study, we applied both TMS and LIFU stimulations to the human Frontal Eye Field (FEF) for modulating the eye movement behaviour. Two healthy subjects were recruited and performed a standardised pro- and anti-saccade experiment. In the TMS experiment, 25% of trials were randomly selected and subject's left FEF was stimulated using a single TMS pulse with an intensity of 2.7 T at 100 ms after the target onset. There were significant effects of TMS on a) increasing the latency of the pro-saccade to both sides ($p < 0.001$), b) increasing anti-saccade latency on ipsilateral side ($p < 0.05$) and c) reducing the erroneous pro-saccades during anti-saccade trials ($p < 0.05$) for both subjects. For

the case of LIFU experiment, we applied a pulsed LIFU sonication with a duty cycle of 50%, 500 Hz pulse repetition frequency, 1 ms tone-burst duration and a spatial-peak pulse average acoustic intensity of 10.6 W/cm^2 at -100 to 200 ms with respect to the target onset while subjects were performing the same pro- and anti-saccade test with 25% to 50% frequency. The value of the acoustic intensity used is in compliance with the international electrotechnical commission (IEC) 60601 part 2 standard for physiotherapy equipment. We observed that the LIFU-mediated neuromodulatory effects only appeared in one subject who showed much higher responses to TMS than the other subject. A significant effect on the pro-saccade latency ($p < 0.05$) was observed with a significant reduction in the erroneous pro-saccade ($p < 0.01$) only on the ipsilateral side. To the best of our knowledge, this is the first study reporting the neuromodulatory effect of LIFU on human FEF. We showed that LIFU on human FEF can modulate the eye movement behaviour. The observed discrepancies between TMS and LIFU stimulations might be due to the conservative choice of the acoustic intensity of LIFU. The subject-dependency on neuromodulatory effect to LIFU warrants further study on subject-specific acoustic simulation.

Disclosures: **H. Kim:** None. **K. Pahk:** None. **S. Yeo:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

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Program#/Poster#: 060.16/DD7

Topic: E.01. Eye Movements

Support: NIH U01-NS094330

Title: Spatial cueing and planned saccade tasks in the marmoset

Authors: *S. H. COOP, G. W. BUNCE, J. F. MITCHELL
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Abstract: - The common marmoset has recently attracted interest as a model for visual neuroscience. The organization of their visual and oculomotor systems is highly similar to other primates with a particular advantage that most cortical areas (FEF, MT, etc⋯) are accessible at the surface enabling imaging and array recordings. The macaque is the leading animal model for the study of eye movements, spatial working memory, and covert attention. Much less is known about these behaviors in the marmoset under similar task contexts. Here we introduce a behavioral task that uses a central cue at fixation to direct a delayed saccade to one target among equally spaced peripheral distracters. This lays a foundation for studying neural mechanisms of eye movement planning and its influence on perception in this species.
- Two marmosets learned to plan saccades based on a line cue presented at fixation. Monkeys

were first trained to maintain fixation for a delay while 4 moving dot fields faded into the periphery. After marmosets had learned to hold fixation for 600-750ms, we then introduced "cued" trials that briefly displayed a salient line at fixation which pointed towards one of the moving dot fields (50-200ms cue duration, 1-2 degrees line length, 5 degrees target eccentricity). The fixation point offset acted as a "go" cue for a saccade to the target aperture, which if executed, gave a larger reward than fixation alone. Initial training was facilitated by using a line cue that connected the fixation point to the peripheral aperture, which was then reduced in length over training. Each monkey learned to complete on average 200-400 trials per day with minimal spatial bias and an average performance above 60-80% correct. By varying how early the line cue was presented we also determined how their performance varied with delay period length.
- Saccadic eye movements made to the target aperture were influenced by the target's stimulus motion. We observed smooth pursuit with a 10-20% gain of the stimulus motion in the target aperture which was present within 50ms following saccade offset. This suggests that pre-saccadic selection involves read-out of motion from the target aperture which can lead to priming of early post-saccadic pursuit.

Disclosures: **S.H. Coop:** None. **G.W. Bunce:** None. **J.F. Mitchell:** None.

Poster

060. Eye Movements: Saccades

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Topic: E.01. Eye Movements

Support: NIH Grant EY022854

Title: Population activity in the superior colliculus for saccades to moving targets

Authors: *K. J. MOHSENIAN[1], A. L. CECALA[2], N. J. GANDHI[1]
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Abstract: The ability to intercept moving targets is crucial for both survival and success. The superior colliculus (SC), a central hub for sensory-motor integration, issues the movement command to produce saccadic eye movements. For saccades to stationary targets, the SC population activity is characterized as a Gaussian distribution. The SC contributes to the generation of saccades to moving targets also, but its exact role in not clear. In particular, afferent and efferent delays in neural transduction cause the sensory representation of a moving target's position to lag its actual position by 50-100 msec. Target motion during this delay must be accounted for in order to direct action to its future location. Previous work recording single units in the SC reported that some neurons issue the saccade command to a target's location 50-

100ms prior to saccade onset. Incidentally, other SC neurons seem to account for the neural transduction delay, reflecting activity for the executed saccade vector. Our objective here is to determine the population activity of the SC for saccades to moving targets. To address this knowledge gap, we recorded neural activity from a rhesus monkey which performed a delayed saccade task. The delay period, initial target location, target speed (range: 15-60 deg/s) and target direction (inward, outward) were varied randomly to elicit saccades with different vectors (amplitude and angle). Trials using stationary targets and moving targets were randomly interleaved. SC population activities of the two trial types were compared through matching the saccade vector performed by the subject. Preliminary results lend support to an alternative view - namely that the SC population activity, when the target is moving, is not Gaussian. We will assess whether the non-Gaussian population can be used to differentiate between prominent algorithms (weighted vector summation vs. weighted vector averaging) for decoding SC activity for saccade generation.

Disclosures: K.J. Mohsenian: None. **A.L. Cecala:** None. **N.J. Gandhi:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.18/DD9

Topic: E.01. Eye Movements

Support: NIH Grant 5G12MD007603

Title: Local and global spatial references for guiding saccades to remembered locations in crowded visual scenes

Authors: *J. A. EDELMAN[1], S. MOHAMMAD[2]
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Abstract: Saccadic eye movements can be used to revisit items of interest in periphery of a crowded visual scene quickly, including items that are very difficult to see from a distance. Thus, re-fixation must require a combination of vision and spatial memory. This raises the question of what type of spatial memory is used. One possibility is that the target's location relative to local landmarks is memorized; a second is that its location relative to the entire visual scene is memorized. We addressed this by recording EMs in 4 Ss (Eyelink II, SR Research, 500 Hz) performing a visual search task requiring high-acuity and precise target fixation, with varying spatial relationships between target, local landmark, and visual scene. Visual stimuli were controlled using Experiment Builder (SR Research), and were presented on a 22'' CRT monitor controlled by a Windows PC. In each trial, subjects had to make saccades between the far left

and right sides of the display. On each repeated visit to one side of the screen (left or right on separate blocks of 24 trials), Ss had to find a small numeral (1-9) buried in a rectangular array of letters (21 rows of letters; 21 letters per row) and indicate its identity with a keypress. Trials were run in 3 conditions: 1) Local/global fixed: numeral position within text array and text array position within computer display were held constant within a block of trials. 2) Local fixed: numeral position within text array held constant, but text array shifted vertical position across trials. 3) Global fixed: numeral position within display held constant, but position within text array (and thus position of text array within display) shifted vertical position across trials. We calculated mean search time (MST) as well as the mean distance between the endpoint of the primary saccade traversing the screen and the spatial position of the numeral (MED). MSTs for the conditions 1-3 above were, respectively, 2.42, 2.53, and 3.39 msec. MED were 1.47, 1.67, and 2.46 deg. These data support the idea that local spatial references play a much powerful role than global references in governing saccadic re-fixations in crowded visual scenes.

Disclosures: **J.A. Edelman:** None. **S. Mohammad:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

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Support: NEI RO1-EY08890

NEI P30-EY008126

U54-HD083211

Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience

Title: Metaclustering: A novel method for identifying robust classes of neuronal responses in frontal eye field

Authors: *K. A. LOWE[1], J. D. SCHALL[2]
[2]Psychology, [1]Vanderbilt Univ., Nashville, TN

Abstract: The frontal eye fields (FEF) are known to be intimately involved in cortical control of eye movements. However, the neuronal responses in this area have largely been characterized simply as “visual,” “movement-related,” or “visuomovement” (Bruce & Goldberg 1985). This classification scheme has proven fruitful, and has been used to understand some of the information processing that occurs in FEF (e.g., Purcell et al 2012). However, these definitions do not account for the additional variety that has been observed in more complex tasks (Sato et al

2001, Sato & Schall 2003, Ray et al 2009). While the traditional classification is useful, it is clearly too broad to fully explain FEF function. In order to untangle groups of neurons that are traditionally considered to be in the same class, but seem to have distinct response properties, I have applied a modern computational technique to data recorded from FEF: cluster analysis. This technique is able to identify nuanced differences in neuronal response profiles, and reveals that there are more than the three traditional groups. However, cluster analysis requires the selection of a number of parameters, in particular a distance metric. It is also sensitive to the input data, in this case the method by which each unit's spike density function is summarized. We used three distance metrics: Euclidean distance, correlation distance, and a multiplicative analog of Euclidean distance ("Euclidean product"), and summarized the spike density functions by calculating either the mean firing rate during key task epochs, the slope of the SDF during the epochs, or both means and slopes. Each combination of parameters produced groups that were different than the traditional groups and similar (but importantly, not identical) to each other. Because there is not a principled way to select the appropriate combination of distance metric and summarization method, I introduce a new technique that combines the results of several individual clustering schemes without having to make decisions regarding which clustering parameters to use. This technique, "metaclustering," reveals at least seven robust groups of neurons with distinct response properties, including several different types of "visual" cells and previously unreported cells with an "off" response to visual stimulation. By identifying and understanding these additional, separate groups, it is possible to have a more comprehensive understanding of the cortical microcircuitry that controls eye movements. Additionally, the technique itself is portable in that it can be used to analyze any similar dataset and dissect microcircuitry throughout the brain.

Disclosures: **K.A. Lowe:** None. **J.D. Schall:** None.

Poster

060. Eye Movements: Saccades

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Topic: E.01. Eye Movements

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NIH RO1-EY08890

NIH P30-EY008126

NIH U54-HD083211

Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience

Title: Neural correlates of speed-accuracy tradeoff: Superior colliculus and frontal eye field

Authors: *T. REPPERT, M. SERVANT, R. P. HEITZ, J. D. SCHALL
Psychology, Vanderbilt Univ., Nashville, TN

Abstract: The speed-accuracy tradeoff (SAT) governs decision-making and movement execution. Neurophysiological correlates of SAT have been reported in the frontal eye field (FEF), lateral intraparietal area as well as premotor and motor cortex. Here we report new observations from the superior colliculus (SC) of macaque monkeys performing visual search with interleaved cues emphasizing FAST or ACCURATE responses. Saccade vigor measured now in four monkeys was invariant in FAST and ACCURATE trials. As observed previously (Heitz & Schall 2012) and replicated now in another monkey in the FEF and two monkeys in SC, speed-accuracy tradeoff was accomplished through several distinct neurophysiological adjustments. We compared modulation in SC and FEF, with the following results: (1) Like FEF, during the fixation interval before search array presentation, discharge rates in SC tended to be higher during FAST relative to ACCURATE trials. (2) Unlike FEF, the initial visual response to the search array in SC was invariant during FAST and ACCURATE trials. (3) Like FEF, the duration of target selection tended to be longer in ACCURATE than in FAST trials. (4) Unlike FEF, the discharge rate immediately before saccade initiation to the target of the search array was invariant during FAST relative to ACCURATE trials. (5) Extending previous analyses, we now report that activity in FEF and SC during the fixation interval and after array presentation predicted directional errors. (6) Activity in SC just before saccade onset predicted peak saccade velocity. These new results replicate and extend previous findings, guide refinements of neuromimetic models of perceptual decision-making, and inform our understanding of the neural basis of general stochastic accumulator models.

Disclosures: **T. Reppert:** None. **M. Servant:** None. **R.P. Heitz:** None. **J.D. Schall:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

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Topic: E.01. Eye Movements

Support: F32-EY023922

F32-EY23526

T32-EY07135

R01-EY8890

R01-MH55806

P30-EY08126

U54-HD083211

Title: Functional architecture of frontal eye field: Spatial clustering of functional properties

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Abstract: The columnar organization of functional properties is a well-known, fundamental property of many cortical areas in occipital, parietal and temporal lobes. Some evidence of columnar anatomical structure have been reported for frontal lobe areas, but information about organization of functional properties is lacking. Therefore, using linear electrode arrays with 24 (Plexon) or 32 (Neuronexus) contacts (100 µm, 150 µm, or 200 µm spacing), we sampled neural activity in the frontal eye field associated with visual responses and saccades. Penetrations through the rostral bank of the arcuate sulcus sample neural activity predominantly but not exclusively tangential to the cortical layers. We quantified the degree of similarity of neural modulation aligned on target presentation and aligned on memory-guided saccade across adjacent recording contacts in a current sample of 64 total penetrations in 4 macaque monkeys. In the current sample we found ~130 clusters of common modulation patterns in ~45 individual penetrations sampled for each monkey. Of these, ~60 spanned more than just 2 adjacent contacts. Clusters measured on average (±SD) ~400 (340) µm. In ~32 penetrations multiple clusters were found. Spacing between clusters measured on average (±SD) ~375 (400) µm. Further research is needed to determine how the clustering we observed is related to the laminar organization of frontal eye field. These new observations demonstrate that a columnar as well as laminar functional architecture can be described for frontal eye field.

Disclosures: J.G. Elsey: None. **K. Lowe:** None. **P. Middlebrooks:** None. **J.D. Cosman:** None. **J.D. Schall:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 060.22/DD13

Topic: E.01. Eye Movements

Support: CAS Hundred Talent Program

Title: Dissociable effects of superior colliculus imbalance on microsaccade direction and frequency

Authors: *G. YU[1], P. BAO[2], Q. TIAN[2], M. YANG[2], M. C. DORRIS[2]
[1]Inst. of Neuroscience, Shanghai, Shanghai, China; [2]Inst. of Neurosci., Shanghai, China

Abstract: Microsaccades are tiny ballistic eye movements that occur during attempted gaze. Behavioral studies indicate their direction and/or frequency are modulated by many sensory and cognitive processes. The neural mechanism underlying these microsaccade related effects, however, is poorly understood. Here, monkeys engaged in 3 different behavioral contexts (ocular fixation, saccade decision making and presentation of visual transients). Simultaneously we recorded or applied microstimulation to neurons across the primate superior colliculus (SC) map. The SC has been shown to be crucial for microsaccade generation and we hypothesized that it would similarly be involved in their contextual modulation. We had 3 main findings. 1) During a fixation task, we imbalanced activity across the SC map directly via microstimulation. To begin, we aimed to observe how microsaccade direction and frequency were affected by directly perturbing SC activity under a neutral fixation condition. At low levels of stimulation, microsaccade frequency was not affected but direction was biased towards the stimulation site. This direction bias became more pronounced until a threshold level of stimulation was reached after which large macrosaccades were directed to stimulation site immediately after stimulation onset. 2) During a saccade decision making task, we recorded activity across the SC map. Neural activity became increasingly imbalanced in favor of the final saccade direction as the decision deadline approached. Following a similar time course as this neural imbalance, microsaccade direction became biased towards the site of SC imbalance while frequency decreased. 3) During the presentation of visual transients, we applied sub-threshold stimulation to the SC map. The visual transients were presented either on the same or opposite location relative to the stimulation site. Microsaccades were consistently biased towards the stimulation site regardless of the congruency with the visual transient. However, microsaccade frequency increased primarily when the visual transient was opposite to the stimulation site. In conclusion, we show that microsaccades are consistently biased towards locations associated with increased SC activity across all our behavioral contexts. However, the relationship with SC activity and microsaccade frequency was more complicated and depended on behavioral context. Our results provide direct evidence that imbalances in SC activity contribute to previously documented sensory and cognitive effects on microsaccades direction and indicate effects of microsaccade direction and frequency can become dissociable under some conditions.

Disclosures: G. Yu: None. **P. Bao:** None. **Q. Tian:** None. **M. Yang:** None. **M.C. Dorris:** None.

Poster

060. Eye Movements: Saccades

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: E.01. Eye Movements

Support: DBT/IISc Grant

Title: Central and peripheral correlates of eye movement planning

Authors: S. P. RUNGTA, *A. N. MURTHY
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Abstract: A hallmark of human behaviour is that we can either couple or decouple our thoughts, decision and motor plans from actions. Previous studies have reported evidence of gating of information between intention and action that can happen at different levels in the central nervous system involving the motor cortex, subcortical structures such as the basal ganglia and even in the spinal cord. To examine the extent of this gating we collected data from neck muscles and neural recording from frontal eye field (FEF) in macaque monkeys involved in preparing for saccadic eye movements in a memory guided task. The delay period in this tasks separates 'where' from 'when' to initiate a saccade. The information prior to the delay time could be used during the interval to plan for an upcoming movement. We observed that significant number of units show modulation during this delay period in FEF and neck muscles. The study was done under head constrained conditions to ensure no neck movements were being made during this time interval, suggesting that some information leaks through into the periphery while planning the saccade. Interestingly, even though we observed modulations during the delay period in periphery it could not be used to infer the direction of an upcoming movement. However, the activity during this interval was correlated with the time it took to initiate saccades. Since accumulation to threshold has been associated with motor preparation in the FEF, we tested whether this same framework could be extended during the delay time to explain the recruitment of motor units. Our results reveal that we can assess some aspects of central planning in the activity of motor units using these accumulator frameworks.

Disclosures: S.P. Rungta: None. **A.N. Murthy:** None.

Poster

060. Eye Movements: Saccades

Location: Halls A-C

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Program#/Poster#: 060.24/DD15

Topic: E.01. Eye Movements

Title: Sensorimotor transformations in monkeys under scotopic and photopic conditions

Authors: *O. SPIVAK[1], P. THIER[1], S. BARASH[2]
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Abstract: In darkness, foveal cones are insensitive. Yet, the oculomotor patterns of monkey photopic vision such as the sequences of fixation intervals and saccades persist in scotopic vision. We follow the hypothesis that a rod-dense region (RDR) in the superior retina could substitute for the fovea during scotopic vision. If the RDR is directed to the target, the fovea´s line is directed above the target. Exactly this effect, an apparent gaze upshift, exists in monkeys in the dark and its extent greatly increases with dark adaptation. However, the upshift can be seen already shortly after the onset of darkness, whereas scotopic vision starts much later. Hence, while the upshift is part of scotopic vision, probably deployed to use the RDR for fixation, it cannot be a direct consequence of the relative weight of rod vision. Rather, the upshift seems to reflect a switch between two fixation strategies, a first one serving the fovea and a second one the RDR. Here we ask if this switch involves other oculomotor behaviors, in particular saccades, in a way that would be consistent with the RDR hypothesis. We thus predicted that scotopic saccades would be based on different sensorimotor transformations from photopic saccades. The null hypothesis, that scotopic and photopic saccades are based on the same sensorimotor transformations, leads to the prediction that scotopic saccades would end with the fovea on the target, regardless of their starting position. We tested this in 2 monkeys using centrifugal saccades with target positions on the horizontal axis. In this way, the starting positions of all saccades have the same upshift. The null hypothesis was rejected: scotopic saccades did not end with the fovea on the target. Rather, both start and end points of the saccades were upshifted, though the deviation from pure horizontal direction varied between monkeys. Scotopic saccade endpoints are more scattered - in line with the larger area of the RDR, compared to the fovea. The scotopic sensorimotor transformations have converted one upshifted location to another, though precision varies. Thus, scotopic saccades are guided by specialized sensorimotor transformations consistent with the RDR hypothesis. What brain circuitry underlies scotopic sensorimotor transformation? We started to probe this question by studying the effects of microstimulation of the superior colliculus (SC) deep layers. Initial results from one monkey appear to suggest that the SC is downstream from the generation of the upshift—surprisingly, as Stanford and Sparks 1994 reported that the analogous upshift of memory saccades is generated downstream of the SC.

Disclosures: O. Spivak: None. **P. Thier:** None. **S. Barash:** None.

Poster

060. Eye Movements: Saccades

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Title: Sensory cue processing time modulates LIP neuronal activity in parallel with urgent choice accuracy

Authors: *J. SEIDEMAN, E. SALINAS, T. R. STANFORD
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Abstract: It is well established that, on average, the firing rates of neurons within the lateral intraparietal area (LIP) of monkeys performing a random-dot direction-discrimination task ramp upwards or downwards depending on the direction of the impending choice, with a slope that depends on the strength of the motion stimulus. This characteristic ramping activity is posited to represent the temporal integration of sensory evidence governing the formation of a perceptual decision. However, without directly comparing changes in LIP activity to a behavioral metric that can accurately define the formation and development of a perceptual judgment in time, this hypothesis remains largely unsubstantiated. Here, we recorded from single neurons within area LIP while monkeys performed a variety of simple perceptual discrimination tasks under urgent circumstances (i.e., compelled paradigms) in which saccadic choice accuracy ranged from chance to near 100% correct as a function of processing time – the maximum amount of time available to perceptually process sensory information prior to movement onset. We observed processing-time-dependent changes in LIP activity that evolved in parallel with the measured psychophysical changes in choice performance, which increased above chance levels within 150 ms of cue onset. Initial comparisons between trials with different stimulus manipulations suggest that the LIP modulation is strongly dependent not only on temporal constraints, but also on the attentional demands (e.g., top-down vs. bottom-up) imposed by the task. These preliminary data begin to delineate how LIP contributions to an informed motor choice depend on both when and how a perceptual judgment is carried out.

Disclosures: **J. Seideman:** None. **E. Salinas:** None. **T.R. Stanford:** None.

Poster

061. Cortical Planning and Execution: Human Neurophysiology

Location: Halls A-C

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Topic: E.04. Voluntary Movements

Support: NIH 5R01EY015545-12

Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech

Boswell Foundation

Title: Forward estimation of movement state in the human posterior parietal cortex: A single neuron recording study with a tetraplegic participant

Authors: *V. N. CHRISTOPOULOS[1], S. SAKELLARIDI[1], T. AFLALO[1], K. PEJSA[1], E. ROSARIO[2], D. OUELLETTE[2], N. POURATIAN[3], R. ANDERSEN[1]
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Abstract: Humans and animals select actions based on noisy sensory information and incomplete knowledge of the environment. To avoid instabilities due to these factors, the brain uses internal forward models to predict how ongoing actions affect the state of the body and the environment. The predictions are integrated with incoming sensory information to update the estimate of the next state. A recent study in our lab showed that area 5d of the posterior parietal cortex (PPC) contains an internal estimate of the movement kinematics that is updated via perceptual feedback. Specifically, two non-human primates (NHPs) performed reaches using a virtual reality setup, while neuronal activity was simultaneously recorded from area 5d. In some trials, an artificial visual lag between hand and cursor position was introduced. We found that the neural signal in 5d was correlated to real-time hand kinematics, but this correlation was immediately diminished after the lag onset. As the sessions progressed, area 5d readapted to visual lag perturbation and the correlation was re-established to the pro-perturbation level. Here, we explore whether such an internal model exists in the human PPC. We recorded neuronal activity from a participant with tetraplegia (C3-C4 10 years post injury) who is implanted with a 96 channel microelectrode array in the anterior intraparietal (AIP) cortex. The participant was trained to control a cursor with her head and performed center-out movements to eight peripheral targets. Head location was recorded by placing a magnetic tracker (3D Guidance trakSTAR, Ascension Technology Corp) on her chin. To test whether the recorded AIP population activity is sensitive to delayed visual feedback, we introduced an artificial visual lag of about 450 ms between head and cursor location. By performing a regression analysis between the movement velocity and the recorded neuronal activity, we found a significant drop of R^2 immediately after the visual lag onset. The participant compensated for the delayed visual feedback by slowing down the movements. As the session progressed, the R^2 gradually increased to about the original level. During washout, AIP readapted and R^2 returned to its original level. These preliminary results suggest that human AIP is sensitive to altered sensory feedback, but it is capable of adapting and compensating for perturbations after prolonged exposure. We interpret these results as evidence that AIP in humans and NHPs contains an adaptive internal estimate of the current state that compensates for the delayed visual feedback.

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Poster

061. Cortical Planning and Execution: Human Neurophysiology

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Craig H. Neilsen Foundation Grant 261299

Title: Gating of somatosensory evoked potentials during precision and power grip in humans

Authors: *R. A. OZDEMIR[1,2], M. A. PEREZ[1,2]
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Abstract: Evidence showed that the primary motor cortex contributes to a different extent to the performance of power grip and precision grip (Federico and Perez, 2016; Tazoe and Perez, 2017). The contribution of the somatosensory cortex to these different grasping configurations, however, remains largely unknown. In the present study, we measured somatosensory evoked potentials (SSEPs; P14/N20, N20/P25, and P25/N33 components) using electroencephalographic recordings over the somatosensory cortex and electrical stimulation of the ulnar nerve at the wrist (at an intensity of 10% of the maximal motor response) at rest and when the first dorsal interosseous muscle performed 5%, 15%, and 30% of maximal voluntary contraction (MVC) during index finger abduction, precision, and power grip in 19 healthy volunteers (30.7±9.8 years, 7 females). We found that the amplitude of all SSEP components was suppressed during power grip compared with index finger abduction and precision grip with increasing level of force. The suppression of all SSEP components was more pronounced during 30% of MVC compared with the other force levels. Note that during power grip with increasing level of force sensory gating was more pronounced for the P14/N20 and N20/P25 SSEP components, suggesting that cortical and subcortical mechanisms contributed to these effects. Thus, our findings suggest that a more pronounced gating of sensory input may be achieved when humans perform a power grip. This is consistent with recent results showing that cortical inputs make a distinct contribution to gross and fine dexterous finger manipulations.

Disclosures: R.A. Ozdemir: None. **M.A. Perez:** None.

Poster

061. Cortical Planning and Execution: Human Neurophysiology

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Craig H. Neilsen Foundation Grant 261299

Craig H. Neilsen Foundation Grant 454590

Title: Altered sensory gating during voluntary activity in humans with spinal cord injury

Authors: *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: In intact humans, the somatosensory cortex (S1) gates afferent input contributing to filter irrelevant signals during a motor behavior. The role of the S1 in sensory gating in humans with spinal cord injury (SCI) remains largely unknown. Here, we examined somatosensory evoked potentials (SSEPs; P14/N20, N20/P25, and P25/N33 components) using electroencephalographic recordings over the S1 and electrical stimulation of the ulnar nerve at the wrist (at an intensity of ~10% of the maximal motor response) at rest and during 30% and 70% of isometric maximal voluntary contraction (MVC) into index finger abduction in individuals with incomplete chronic cervical SCI and in uninjured controls. SSEPs had prolonged latencies in SCI subjects compared with controls (P14/N20 by 1.9±1.6 ms, N20/P25 by 2.6±1.1 ms, and P25/N33 by 2.1±1.4 ms). We found that the amplitude of the P14/N20, N20/P25, and P25/N33 SSEP components decreased during voluntary activity compared with rest and to a larger extent during 70% compared with 30% of MVC in control subjects. In SCI subjects, the amplitude of all SSEP components decreased, to a larger extent than in controls, during 30% (P14/N20: control=91.2±18.5%, SCI=72.6±19.7%; N20/P25: control=85.3±13.0%, SCI=75.6±16.5%; P25/N33: control=87.5±27.3%, SCI=76.3±24.5%) and 70% (P14/N20: control=79.7±15.6%, SCI=65.3±26.5%; N20/P25: control=76.2±13.2%, SCI=63.7±11.2%; P25/N33: control=78.7±22.6%, SCI=64.7±21.2%) of MVC compared with rest. Notably, our

findings suggest that during tonic voluntary activity humans with chronic incomplete SCI gate sensory input to a larger extent than control subjects.

Disclosures: Y. Lei: None. **M.A. Perez:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: 15H01846

15K21602

Title: Motor engram as dynamic change of the cortical network during early sequence learning: An fMRI study

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Abstract: Practice improves motor skill performance which is characterized by speed and accuracy. While practice with speed pressure defines a particular difficulty level to yield optimal information for the learning, even without speed pressure, implicit learning is known to occur. Little is known how these characteristics of the practice, the speed or accuracy, are integrated to form the neural substrates of the sequence learning, that is, engram. Engram has dormant and activated states. Previous neuroimaging approaches to find out the motor engram have mainly focused on the ecphory because they utilized task-related activation to evaluate the effect of learning. Here we utilized eigenvector centrality (EC) as the measure of the information transfer at the network level accumulation that characterize both states of engram. We conducted functional MRI with 58 normal volunteers using sequential finger tapping task with their non-dominant left hand. Participants exercised a sequence as fast as possible (maximum mode) or with constant speed by a visual cue (2 Hz, constant mode) alternately. Our hypothesis was that sequential movement of different learning modes enhanced distinct engram. We applied EC to the residual time-series after modeling out the task-related activity. Performance was transferred from the constant mode to maximum mode, but not vice versa. During the maximum mode, the engram was found in in the left anterior intraparietal sulcus (aIPS) connected with the ventral inferior parietal lobule (IPL). During the constant mode, the distinct engram was found in bilateral dorsal premotor cortex and right primary motor cortex (M1).The learning-related increment of the task-related activities of the right M1 was observed in both modes. Thus the

motor engram of the sequential finger tapping is formed in the M1-centered parietal-premotor network. The left aIPS-IPL represented the sensorimotor integration of precisely tuned rapid finger movements the one finger to the next in the sequence. PMd is a probable substrate for the coordinate transformation from the visually presented spatial goals to joint movements in the response domain through associative learning, coding the accuracy with the M1. This is the first study revealing the dynamic change of the motor engrams distributed in the M1-centered motor hierarchy which were formed with 30 min training.

Disclosures: Y.H. Hamano: None. **S.K. Sugawara:** None. **N. Sadato:** None.

Poster

061. Cortical Planning and Execution: Human Neurophysiology

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 061.05/DD21

Topic: E.04. Voluntary Movements

Title: Supplementary motor area activity at rest and during finger tapping in young adults with developmental dyslexia

Authors: *A. L. SMILEY-OYEN, E. VANSICKLE, E. PETRAN, E. STEGEMOLLER
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Abstract: Developmental dyslexia (DD) is generally viewed as a disorder involving phonetics, with the underlying cause that of poorly processing sound. Many people with DD also exhibit difficulties with the temporal aspect of movement sequencing. It is well established that the pre-supplementary motor area (SMA) and SMA are involved in motor planning and execution of movement sequences. Interestingly, the broad network for sound processing also involves preSMA/SMA. In fact, one position is that the preSMA/SMA serves as part of a larger cortical-subcortical *temporal processing network* that underlies processing sound (Kotz et al., 2010, Schwartz et al., 2012; Schwartz et al., 2011). Given the involvement of the preSMA/SMA in movement sequencing, it is feasible that this temporal processing network also impacts movement sequencing. The purpose of this study was to examine EEG activity over the preSMA/SMA while at rest and during finger tapping in young adults with and without DD. It has been found that children with DD exhibit a dominance of theta band activity (4-7 Hz) when at rest, which was interpreted as abnormal hypoarousal mechanisms. We hypothesized that theta band activity would be greater in young adults with DD during rest and during finger tapping. Participants were age- and gender-matched, and all were right-handed. They engaged in three conditions: sitting quietly at rest with eyes open, tapping with their right-hand index finger in synchrony with a tone at 70 bpm, and doing the same at 140 bmp. Analysis focused on EEG collected from electrode Cz, the electrode over the area of the preSMA/SMA. The power spectrum pattern of results supported our hypothesis. Theta activity at Cz was higher in those

with DD at rest as well as during tapping at both rates. We interpret these data as support for the position that the hypoarousal found in children with DD continues into adulthood. These data provide baseline information for further study of the role of the preSMA/SMA in movement sequencing in people with DD.

Disclosures: A.L. Smiley-Oyen: None. **E. VanSickle:** None. **E. Petran:** None. **E. Stegemoller:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: Grants-in-Aid for Scientific Research (C) (25350594)

Grants-in-Aid for Scientific Research (C) (17K01503)

Title: Cerebral hemodynamic responses during the alternating lower limb movement with robot suit hybrid assistive limb (HAL)

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Abstract: Robotic devices have been receiving attention in rehabilitation medicine. The hybrid assistive limb (HAL) is one of the wearable robot suits assisting limb movements by detecting bioelectric signals from skin electrodes, and it might promote motor learning. We investigated the effects of the HAL on brain activity during lower limb exercise. Healthy subjects sat on a backless chair and were required to execute leg extension/flexion exercise alternately in the right and left sides for 20 sec. The subjects performed the tasks with three different conditions randomly; 1) under HAL assist (HAL task), 2) under 1kg-weight load on the ankle (weight task), and 3) without weight condition (no weight; basal task). During the tasks, we measured oxygenated-hemoglobin (oxy-Hb), deoxy-Hb and total-Hb concentrations using Near-Infrared Spectroscopy (NIRS) in regions of interest (ROIs) in the cerebral cortex; anterior dorsomedial prefrontal cortex (aDMPFC), right and left dorsolateral prefrontal cortex (DLPFC), supplementary motor area, premotor areas, primary motor areas and primary sensory areas. We also measured scalp hemodynamic activity over the right and left sensorimotor cortex, which was subtracted from the hemodynamic responses in each ROI. Subjects were also required to report a sense of HAL-use by visual analogue scale. The results showed that hemodynamic

activity was significantly higher in the HAL task than the weight task in the right primary sensory area, while there were no significant differences in the other ROIs. Furthermore, hemodynamic responses were dependent on task difficulty; in the aDMPFC and left DLPFC, the subjects who felt better feeling with HAL-use showed increased hemodynamic responses. The findings indicated that sensory feedbacks were increased in the HAL task, and that activity in the prefrontal regions involved in motor performance (aDMPFC and left DLPFC) was associated with the better sense of HAL-use. The results suggest that application of the robotic device is useful in rehabilitation medicine to lead to a better subjective sense of use during voluntary movements via somatosensory feedbacks.

Disclosures: S. Urakawa: None. **Y. Ota:** None. **K. Takamoto:** None. **T. Ono:** None. **H. Nishijo:** None.

Poster

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Program#/Poster#: 061.07/DD23

Topic: E.04. Voluntary Movements

Support: KAKENHI 15H05874

KAKENHI 17H05907

KAKENHI 26282218

Title: Active engagement of higher-order motor cortices in motor inhibition: Evidence from direct neural recording and stimulation during Go/No-Go paradigm

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Abstract: [Objective] It remains unknown which areas directly inhibit a motor response in a human brain, although previous neuroimaging studies implicated its processing in the medial and lateral frontal areas, especially the pre-supplementary motor area (Pre-SMA), dorsal premotor area (PMd), and ventral premotor area (PMv). The objective of the current study is to clarify and clinically map the key areas in the frontal lobe for motor inhibition.

[Methods] The subjects were 8 epilepsy patients (4 male) with chronic subdural electrode implantation for presurgical evaluation covering the frontal lobe (4 right, 4 left hemisphere) (IRB C533). Event-related potentials (ERPs) were recorded during a Go/No-Go paradigm. 50 Hz electrical stimulation (4-8 mA, 500 ms) was applied to the cortical areas with ERPs specific to No-Go trials (No-Go ERPs). Stimulation was applied in both Go and No-Go trials, and the reaction time and error rate were analyzed. To probe the connectivity from cortical areas with No-Go ERPs, a single pulse electrical stimulation (1Hz, pulse width 0.3 msec, 8-10mA) was applied to those areas, and cortico-cortical evoked potentials (CCEPs) were recorded from the lateral and medial frontal areas.
[Results] No-Go specific ERPs were recorded in Pre-SMA (4/4 patients), PMd (4/4), and PMv (5/5). 50 Hz electrical stimulation was applied to PMd (4 patients), pre-SMA (4), and PMv (3) time-locked to the Go or No-Go trials. Reaction time of Go trials was significantly prolonged by Pre-SMA (3/4), PMd (3/4), and PMv (2/3) stimulation ($p < 0.05$, Wilcoxon test). The error rate of No-Go trials significantly increased by Pre-SMA (1/4), PMd (1/3), PMv (1/3) stimulation, and decreased by Pre-SMA stimulation (1/4). CCEP revealed bidirectional functional connectivity within the No-Go related motor inhibition network, namely, between Pre-SMA and PMd (1/2), and Pre-SMA and PMv (2/2).
[Conclusion] No-Go ERP and CCEP connectivity findings suggested that pre-SMA and lateral premotor areas (PMd, PMv) are most likely involved in motor inhibition each other and that all of them also connect to constitute motor inhibition network. 50Hz electrical stimulation could delineate an active role of these areas in motor inhibition.

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Poster

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Location: Halls A-C

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Program#/Poster#: 061.08/DD24

Topic: E.04. Voluntary Movements

Title: The effects of coordinated vs. uncoordinated whole arm movement on brain-muscle coupling

Authors: L. P. SIMPSON[1], H. NGUYEN[1], S. LEE[2], *S. N. KUKKE[3]
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Abstract: Human beings use their limbs to achieve a wide range of movements. These movements are sporadic and become more controlled over time through motor learning. Additionally, synergies form between muscles to simplify these complex sets of movements into smaller units of movement. The brain and muscles are coupled together; the brain activates various tracts of neurons that cause muscle contraction, and sensory feedback from muscles and joint receptors completes the sensorimotor loop. Neurons in this feedback loop fire in a range of frequencies, and the coupling between neural and muscular signals can be quantified by corticomuscular coherence (CMC). The objective of the study is to study the differences in CMC between movements that are frequently versus non-frequently used, with the assumption that movements made frequently have a higher level of coordination.
Ten healthy adults participated in this IRB-approved study. Electroencephalographic (EEG) and electromyographic (EMG) signals were simultaneously collected during right arm movements using an EEG scalp cap and EMG surface electrodes. Arm movements consisted of extending or flexing the shoulder in one degree of freedom against resistance along a sliding track on a table, while extending or flexing the fingers against resistance from a springs in a specialized glove. Data were collected in four conditions: (1) shoulder flexion and finger extension (coordinated), (2) shoulder flexion and finger flexion (uncoordinated), (3) shoulder extension and finger flexion (coordinated), and (4) shoulder extension and finger extension (uncoordinated). CMC was computed between the C3 electrode (around the sensorimotor area contralateral to the task) and finger muscles (extensor digitorum communis [EDC], and first dorsal interosseous [FDI]) in 10, 7-second trials per condition.
During finger extension tasks (conditions 1 and 3), C3-EDC CMC was not significantly different in the coordinated (0.288 +/- 0.03) and uncoordinated (0.31 +/- 0.03) movements ($F(1,18) = 0.27$, $p = 0.61$). Similarly, during finger flexion tasks (conditions 2 and 4), C3-FDI CMC was not significantly different in the coordinated (0.366 +/- 0.05) and uncoordinated (0.365 +/- 0.05) movements ($F(1,18) = 0.00$, $p = 0.983$). The lack of an effect of shoulder and finger coordination

on CMC in this study may be related to postural shifts of participants during data collection, the small sample size, and the order of attempted trials. Many questions are still unanswered about how CMC plays a role in coordinated movement. Future work will address these questions with a larger number of participants and more controlled experimental conditions.

Disclosures: L.P. Simpson: None. **H. Nguyen:** None. **S. Lee:** None. **S.N. Kukke:** None.

Poster

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Topic: E.04. Voluntary Movements

Title: Short-lasting modulation in corticomotor excitability in response to thermal stimulation of a single digit

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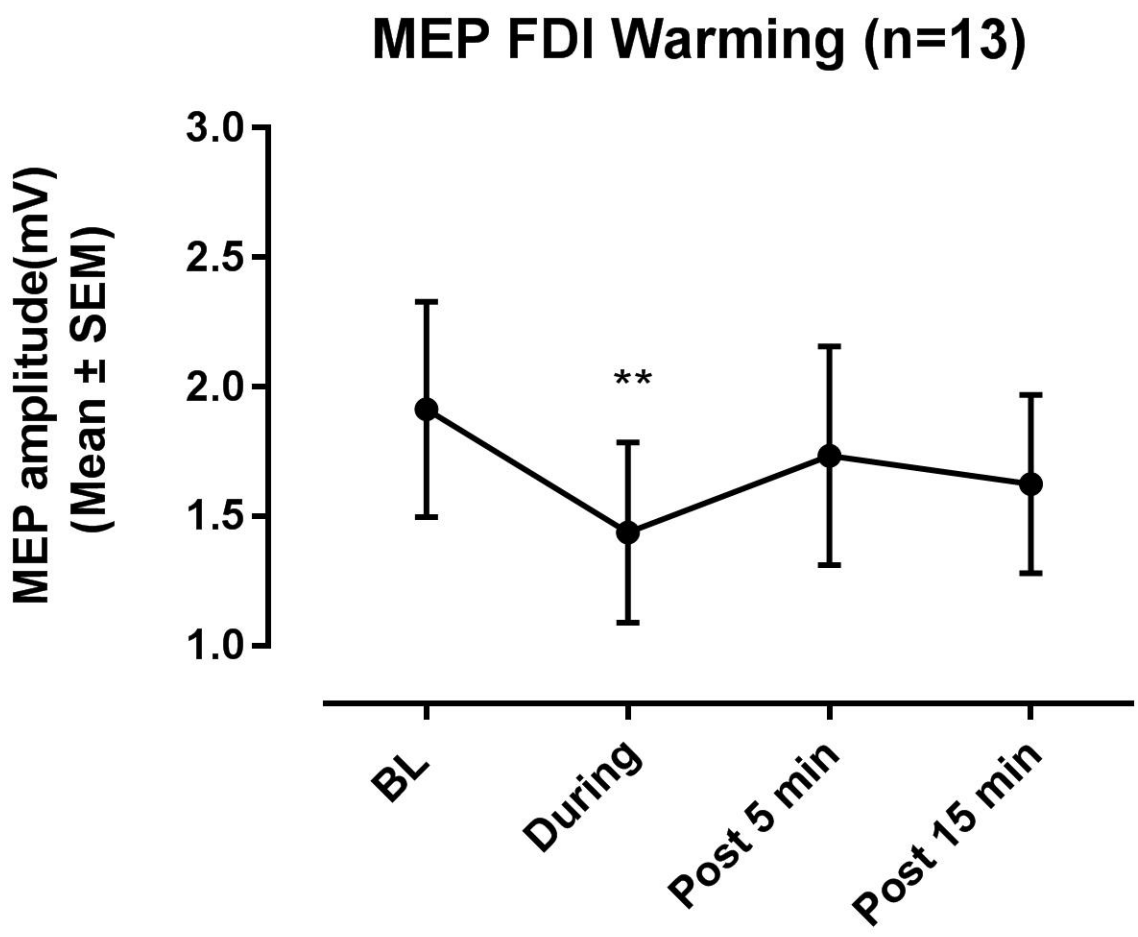
Abstract: There is evidence to suggest that thermal stimulation can assist the recovery of motor and sensory function in stroke survivors (Wu et al. , 2010). However, the neurophysiological basis of thermal effects when applied to extremities remains poorly documented. Here, we report on our early observations regarding the effects of warming stimulation on corticomotor excitability, as reflected in motor evoked potentials (MEPs) induced by transcranial magnetic stimulation. Changes in corticomotor excitability in the hand motor representation (FDI and ADM muscles) were measured (n=15 participants, test intensity=130% rMT) both during and after warming stimulation (T5, T15) of the dominant index finger. The warming was induced using a Torex® finger sleeve gel pack, which was heated to ~46 °C in hot water before application. Within one minute during application (total duration: 5 min), the digital skin temperature significantly increased from baseline (32±2.2 °C vs. 39 ±2.1 °C, $p<0.001$) but rapidly returned to baseline in the post-warming period (T5:33±1.3; T15: 33.4±1.8°C). In parallel, most participants (12/15) exhibited a reduction in MEP amplitude relative to baseline (74± 16%) during the warming while a minority showed an increase. When excluding these atypical responders (n=3), an ANOVA revealed a significant decrease in MEP amplitude during warming (Dunnett' post-test, $p=0.01$) but not in the post-warming period (i.e., T5 and T15). These early observations indicate that thermal stimulation in the non-nociceptive range can modulate corticomotor excitability. In the case of warming stimulation, the modulation seems to be short-lasting and concurrent with the changes in skin temperature. The inter-subject variability is another issue that will require further investigations, especially in relation to gender effects since the three atypical responders were all females.



Disclosures: **Y. Ansari:** None. **A. Remaud:** None. **F. Tremblay:** None.

Poster

061. Cortical Planning and Execution: Human Neurophysiology

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: E.04. Voluntary Movements

Title: Correcting Penfield's Motor Homunculus

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Abstract: One of the most iconic and important images in clinical neurology and neuroscience is Penfield's motor homunculus map illustrating the correspondence between a location on the primary motor cortex and the body area the movement of which is being controlled. For the most part continuity in the motor strip is respected in the map to the area of the body being moved. However, there are some discontinuous jumps in the map; most prominently the hand area is next to the face area in the motor strip even though these are obviously rather distant on the body itself. On Penfield's map the hand is adjacent to the upper face; however, we have seen a number of cases that lead us to believe that this is not the case and instead the lower face is next to the hand. For example, a 65 year-old male presented with left sided weakness, left facial droop, and dysarthria. On examination strength in the right arm, leg and left leg were normal (5/5). Strength in left shoulder abduction and elbow flexion/extension too was 5/5. However, the patient could only extend his wrist to neutral against gravity and had no strength (0/5) in wrist flexion or in any hand muscles. The patient had marked left facial droop and tongue deviation to the left. Other cranial nerves were intact bilaterally as were the left frontalis, orbicularis oculi, and buccinator. Light touch in the left hand, arm, and face was normal as was taste. The patient's MRI showed an acute infarct on diffusion weighted images involving the right precentral gyrus in the hand and upper face region. The patient's muscles of the left lower face, wrist, and hand are severely affected including muscles innervated by two different cranial nerves (left orbicularis oris (CN VII), tongue, (CN XII)). Conversely, upper face muscles, also innervated by CN VII are completely intact. We conclude that the lower face, not the upper face, is next to the hand on Penfield's motor map. As well it would appear on the other side of the hand wrist flexion is next to hand muscles and wrist extension is more rostral, though it will take more cases to confirm this finding. Refined knowledge of Penfield's motor map may be useful for rehabilitation of patients with stroke and other brain lesions as well as understanding neurodevelopment.

Disclosures: **E.L. Altschuler:** None. **N. Ferro:** None. **S.F. Khan:** None. **K. Surapaneni:** None.

Poster

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Topic: E.04. Voluntary Movements

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AFK – CNPq (Proc. no. 303809/2016-7)

Title: The gain of visual feedback influences force variability but not corticomuscular coherence during plantarflexion isometric contractions

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Abstract: Previous studies have shown that visual information interacts with the motor system (visuomotor processing) and optimizes motor performance when more feedback is provided to the subject. One way of changing the amount of visual information is by adjusting the gain of the visual feedback provided during a given motor task. An increased visual feedback gain (VG) enhances force steadiness and accuracy in force-matching isometric tasks. Nonetheless, little is known about changes in the coupling between the motor cortex and a given motor nucleus (corticomuscular coherence, CMC) due to altered VG. The purpose of this study was to investigate the effects of VG on force control and CMC for the soleus muscle. Experiments were carried out on twelve healthy young subjects (8 males, 24-36 yr). Each subject was seated in an armchair with the right leg fully extended and ankle joint at 90deg. The right foot was fastened to a pedal attached to a load cell used to record isometric plantarflexion force. Visual force feedback was provided as a horizontal bar moving up and down on a video monitor positioned 70cm in front of the subject. VG was adjusted by changing the upper and lower limit to the excursion of the moving bar. Three different VGs were adopted, hereafter referred to as high, medium, and low. A fixed horizontal bar at the center of the screen was used to provide the target force level, which was set at 10% or 25% MVC. Tasks were performed with visual feedback provided during the whole trial (50s duration) or only at the beginning (first 12s). Three repetitions were performed for each VG condition in each contraction intensity. Bipolar soleus sEMG and 5-channel EEG (Laplacian filter around Cz) were recorded alongside plantarflexion force. The initial 12s for all the conditions were discarded, and analyses were carried out on the subsequent 30s. Irrespective of contraction intensity, force coefficient of variation, low-frequency (<0.5Hz) force oscillations and beta-band EEG power were significantly higher without visual feedback as compared to visually guided force tasks. Post hoc tests showed that during high VG, force variability and low-frequency oscillations were lower than at low VG. Conversely, no difference was observed in beta-band soleus EMG power and CMC. Additionally, the VG set at the beginning of the trial did not influence motor performance and electrophysiological recordings. These results suggest that the lack of visual feedback increases cortical demand as well as force variability. Also, as VG increases, force variability is reduced, but no significant change is observed in CMC for soleus muscle.

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Poster

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Program#/Poster#: 061.12/DD28

Topic: E.04. Voluntary Movements

Support: NSERC

Title: Magnitude scaling & context-dependency in a rapid visual motor response

Authors: *K. P. CROSS[1], T. CLUFF[4], T. TAKEI[2], S. H. SCOTT[3]
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Abstract: When making goal-directed reaches, proprioceptive feedback generates rapid motor responses to oppose mechanical loads applied to the limb. The fastest motor response generated by proprioception is the short-latency response at ~25ms post-perturbation, but shows limited sensitivity, such as the size of the applied load. Comparatively, the long-latency response at ~60ms is sensitive to behavioural context, such as the target shape and obstacles. Studies have also quantified how shifts of visual feedback of the limb elicit a rapid visuomotor response at ~90ms following the shift. However, few studies have examined if this rapid visuomotor response is influenced by the size of the cursor shift or the behavioural context. We explored this with 3 experiments, all which had subjects reach to a goal (white circle 1cm radius, unless otherwise stated) with hand position represented by a white cursor (0.8cm radius). On random trials we shifted the cursor position lateral to the path from the start position to the goal by ±8cm (unless otherwise stated). Our first experiment used different shift sizes that ranged from 0.5-8cm. Subjects routinely responded to the shift of the cursor with a rapid visuomotor response that started in ~90ms. For the 0.5cm cursor shift, the amplitude of the visuomotor response began to differentiate from corrections to larger-sized shifts in <100ms. Surprisingly, cursor shifts for all but the 0.5cm shift appeared to saturate the earliest visuomotor responses. As a result, the amplitude of corrective responses was similar for >110ms across cursor shifts >1cm. In our second experiment subjects reached for either a narrow (6cm wide bar) or a wide goal (14cm wide bar) in interleaved fashion. When reaching for a wide goal, the initial onset of the visuomotor response was delayed by ~10ms as compared to when subjects reached to a narrow goal. A wide goal also attenuated the amplitude of the visuomotor response for 2cm cursor shifts as compared to a narrow goal, with differentiation occurring in <100ms. In our third experiment, obstacles were present on random trials that blocked subjects from correcting directly to the goal when the cursor was shifted. Surprisingly, we found no differences in the earliest visuomotor responses. In fact, obstacles did not appear to influence the amplitude of visuomotor responses for >130ms after the cursor shift. Our results suggest there are two components to visuomotor

responses: a rapid response that considers some behavioural contexts such as goal properties, followed by a later response that considers a broader range of factors related to behavioural context such as obstacles.

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Poster

061. Cortical Planning and Execution: Human Neurophysiology

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 061.13/DD29

Topic: E.04. Voluntary Movements

Title: The contribution of central mechanisms to motor slowing in humans

Authors: *R. LEHNER, M. BÄCHINGER, S. HANIMANN, C. RYF, F. THOMAS, C. GHIDONI, J. H. BALSTERS, N. WENDEROTH
Dept. of Hlth. and Technol., Neural Control of Movement Lab, ETHZ, Zurich, Switzerland

Abstract: Previous studies showed that repetitive finger tapping at submaximal or maximal speed decreases after approximately 20 s of sustained effort. We reproduced this phenomenon called “motor slowing” for maximal repetitive eye, thumb and foot movements (N = 12, 9, 12, p < 0.025). Further studies from our lab using peripheral nerve stimulation have shown that the decrease in tapping speed cannot be explained by changes distal to or at the neuromuscular junction (N = 9, p > 0.05). We therefore hypothesize that motor slowing is linked to central mechanisms. In a behavioural experiment, we experimentally modulated the resting time (5 s, 10 s, 15 s, 20 s, 25 s, 30 s) between trials of short (10 s) and long tapping intervals (30 s). We showed that the tapping speed recovers as a function of time (N = 18, p < 0.05). This makes it possible to investigate after-effects early after tapping while subjects are at rest.
Here, we present a series of experiments where we used transcranial magnetic stimulation (TMS) or non-invasive neuroimaging techniques (electroencephalography (EEG) / functional magnetic resonance imaging (fMRI)) to better understand which central circuits contribute to motor slowing.
In a first experiment, we measured short latency intracortical inhibition (SICI) over primary motor cortex (M1) during the time course of recovery from long versus short tapping episodes. Our findings indicate that motor slowing is accompanied by significant dis-inhibition of M1 (N = 13, p < 0.05).
In a second experiment, we assessed the spontaneous alpha activity (EEG, 8-12 Hz) over M1 and show that alpha activity recovers more slowly after long than short tapping (N = 17, p < 0.025). Interestingly, when motor slowing was significantly reduced by offering a monetary reward after

20 s, the alpha rhythm desynchronized even more, suggesting that alpha-desynchronization is beneficial for maintaining high tapping speed ($N = 30$, $p < 0.001$).
In a third preliminary experiment using fMRI, we detected differences between long and short tapping in cerebellum and bilateral M1 ($N = 4$, fixed effects model, $p_{FWE} < 0.05$) both during tapping as well as during the rest break.
Our findings suggest that motor slowing is associated with (i) stronger disinhibition of M1, (ii) slower recovery of the spontaneous alpha activity in M1 and (iii) increased haemodynamic response in M1 and cerebellum. However, it is still unclear whether these activity changes in primary motor cortex cause or rather prevent motor slowing.

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Poster

061. Cortical Planning and Execution: Human Neurophysiology

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Program#/Poster#: 061.14/DD30

Topic: E.04. Voluntary Movements

Support: NSERC

CHIR

Title: Dynamic motor encoding of targets in multiple object tracking

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Abstract: Evidence from goal-directed reach planning suggests that, in cases of target uncertainty, the brain specifies, in parallel, multiple potential movements prior to deciding between, and then implementing, one of those movements. In this previous work, motor planning in the context of target uncertainty has only used stationary targets; in many natural situations, however, potential targets of action are continuously moving. Here, using a novel multiple object tracking task, we test the hypothesis that participants unwittingly map multiple competing targets onto the motor commands required to recall their locations, and then non-consciously exploit this motor encoding strategy to improve tracking performance. Participants first viewed a blank screen with two shoot points—linked to sensors held in the left and right hands—one of which is cued (filled-in) as the active shoot point. In the subsequent viewing phase, participants then watched two potential targets: a red target following a complex path and a blue target following a linear path. After blanking the screen and cuing one of the targets, participants reported the

remembered location of the cued target by orienting a 'shooting line' emanating from the shoot point (by applying torque to the associated sensor) and tapping the sensor to fire a 'bullet' along the shooting line. Critically, in all trials, the blue target travelled along a path that either intersected the shooting point or was perpendicular to this intersection point. We hypothesized that if the targets are encoded in motor coordinates (i.e. in terms of the shoot angle), then performance when aiming for the blue target should be better when it moves in line with the intersection line, as the potential shooting angle is constant and does not require updating in working memory. More critically, however, we further predicted that performance on the red target should also be better on these in-line trials, as further working memory resources can be allocated to encoding its location. Consistent with these predictions, we found greater shooting accuracy for both blue and red targets when the blue target was in-line compared to perpendicular. Together, these findings suggest that sensorimotor brain areas are engaged when tracking the positions of visual objects when their locations must ultimately be reported in motor coordinates, and that this natural motor encoding strategy frees-up cognitive resources for optimizing the deployment of limited working memory processes in cases of target uncertainty.

Disclosures: D. Gale: None. **M.J. Carter:** None. **D.M. Wolpert:** None. **J.P. Gallivan:** None. **R.J. Flanagan:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: Huffines Institute Student Research Grant

Title: Failure to enhance post practice consolidation during motor sequence learning using anodal tDCS

Authors: J. CHEN[1], H. KIM[1], T. KIM[1], I. PARK[1], A. T. MCCULLOCH[2], J. J. BUCHANAN[3], *D. L. WRIGHT[4]
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Abstract: Primary motor cortex (M1) is a key neural participant during motor sequence learning. Tecchio et al. (2010) revealed that the application of anodal transcranial direct current stimulation (tDCS) at contralateral M1 immediately following motor training with a serial reaction time task (SRTT) facilitated subsequent test performance of the SRTT compared to a sham control. It was argued that the application of tDCS at M1 facilitated important post-practice consolidation processes critical to offline improvement of the practiced SRTT. Because the test

phase, in Tecchio et al's work, was administered only 15-min after tDCS application, one cannot rule out the possibility that the reported offline performance facilitation was a result of known tDCS after-effects rather than consolidation of the newly acquired motor memory. The present experiments extended the work of Tecchio et al. by including separate experimental conditions that involved a 2-hr rather than just a 15-min delayed retention test following the administration of anodal or sham stimulation at contralateral M1. If consolidation is indeed influenced by this form of non-invasive stimulation protocol then test performance for the trained SRTT should be superior following the anodal compared to sham stimulation condition not only after 15-min but also after 2-hrs. Thirty-two right handed young adults experienced two sets of five blocks with the same SRTT using their left hand. During each block, subjects are required to repeat the required series of keys in the SRTT as accurately and as fast as possible for 30 seconds. Following training, separate participants were exposed to 15-min of 1.0 mA anodal or sham protocol at M1. In the anodal stimulation condition the anode was located on contralateral (i.e., right) M1 while the cathode was located on the right shoulder. Either 15-min or 2-hrs following stimulation participants completed a retention test for the SRTT. Initial assessment of the data revealed the novel finding that anodal stimulation did not result in superior performance for the SRTT test trials compared to the sham condition at 2-hr. A second experiment in which anodal stimulation was administered using bilateral as opposed to unilateral stimulation (i.e., by moving the cathode to ipsilateral M1) did not provide any further benefit for consolidation than observed in the unilateral case. These data, taken together with the extent literature, suggest that temporally disassociating motor training from tDCS stimulation may reduce the impact of exogenously-driven changes in M1 excitability on offline improvement.

Disclosures: J. Chen: None. **H. Kim:** None. **T. Kim:** None. **I. Park:** None. **A.T. McCulloch:** None. **J.J. Buchanan:** None. **D.L. Wright:** None.

Poster

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Location: Halls A-C

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Program#/Poster#: 061.16/DD32

Topic: E.04. Voluntary Movements

Support: Albert Einstein Society

Title: Dexterity modulates ipsilateral motor corticospinal excitability in post-stroke individuals

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Abstract: Unilateral movements are predominantly controlled by the contralateral hemisphere, although ipsilateral motor cortex is known to be engaged depending upon task constraints. One

dimension of task constraints is the dexterity of the motor task. In this study, we investigated the effects of manipulating task dexterity on ipsilateral (to the performing hand) motor cortex representation in patients with stroke. We used transcranial magnetic stimulation (TMS) to quantify motor corticospinal excitability, intracortical inhibition, and cortical facilitation of the ipsilesional and contralesional motor cortex projecting to the contralateral resting extensor carpi radialis (ECR) while participants with unilateral stroke performed unimanual tasks of differing complexity with their ipsilateral active hand. Less dexterous task required the participant to move light-weight plastic balls to specific targets placed 8 inches away using a whole-hand grasp. More dexterous task required participants to move pegs to targets placed 8 inches away using a precision grip. TMS was timed to the beginning of the transport phase of the movement. While the paretic arm was slower than the nonparetic arm, patients performed the less dexterous task with faster speeds compared to the more dexterous task with both arms. ECR activity in the active hand did not significantly differ between tasks, indicating that ECR only played a synergistic role in the task. While performing the tasks of different dexterity with the nonparetic arm, there was no differential modulation of the resting ipsilesional motor cortex. In contrast, task dexterity during paretic hand performance had differential effects on the excitability of the contralesional motor cortex. Compared to the less dexterous task, performance of the more dexterous task with the paretic arm was associated with a greater increase in the excitability of the contralesional motor cortex. Our findings indicate that dexterity requirements of the motor task modulate the role of the contralesional motor cortex during paretic arm performance after unilateral stroke.

Disclosures: S.S. Kantak: None. **D. Luchmee:** None.

Poster

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Program#/Poster#: 061.17/DD33

Topic: E.04. Voluntary Movements

Title: Short-interval intracortical inhibition: The influence of interstimulus interval and current direction

Authors: J. CIRILLO[1,2], *J. G. SEMMLER[3], R. A. MOONEY[1,2], W. D. BYBLOW[1,2]
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Abstract: Gamma-aminobutyric acid (GABA) related inhibition in human primary motor cortex is routinely assessed using the paired-pulse transcranial magnetic stimulation (TMS) paradigm of short-interval intracortical inhibition (SICI). SICI can be assessed in two ways: 1) by expressing the conditioned motor evoked potential (MEP) amplitude to a constant test stimulus

(conventional SICI), or 2) by adjusting the intensity of the test stimulus to maintain a target MEP amplitude in the presence of a conditioning stimulus (threshold tracking SICI). Using both approaches, recent findings indicate that SICI is more robust and sensitive with anterior-posterior (AP) TMS than posterior-anterior (PA) TMS. However, little is known about the influence of interstimulus interval (ISI) and the magnitude of SICI with a AP-induced current or whether the two techniques produce equivalent results. Electromyographic recordings were obtained from the right first dorsal interosseous muscle of 16 participants (20–33 years). SICI was examined across a range of conditioning stimulus intensities (70, 80 and 90% active motor threshold) with ISIs of 2 ms and 3 ms using threshold tracking and conventional paired-pulse TMS for PA and AP stimulation. TMS thresholds were higher for AP stimulation compared with PA ($P<0.001$) and motor evoked potential latency for AP (25.4±1.5 ms) was longer than PA (22.9±1.3 ms, $P<0.001$). SICI assessed using threshold tracking was greater for AP stimulation with an ISI of 3 ms (23.6±9.0%) compared with AP 2 ms (7.5±7.8%, $P<0.001$) and both ISIs for PA stimulation (2 ms 8.6±8.7%, 3 ms 5.9±4.8%; $P<0.001$). An association between conventional and threshold tracking SICI was evident only for PA stimulation with an ISI of 2 ms ($r=0.68$, $P=0.03$). Our findings indicate that SICI assessed with a AP-induced current is sensitive to ISI, with more intracortical inhibition evident using an ISI of 3 ms compared with 2 ms. Furthermore, the mode of action between threshold tracking and conventional SICI may differ depending on ISI and current direction.

Disclosures: J. Cirillo: None. **J.G. Semmler:** None. **R.A. Mooney:** None. **W.D. Byblow:** None.

Poster

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Program#/Poster#: 061.18/DD34

Topic: E.04. Voluntary Movements

Title: Threshold tracking interhemispheric inhibition in healthy adults

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Abstract: Paired-pulse transcranial magnetic stimulation (TMS) can be used to examine interhemispheric transfer. To date, interhemispheric inhibition (IHI) has primarily been assessed using conventional paired-pulse TMS with constant conditioning and test stimulation parameters and posterior-anterior (PA) induced current. However, IHI may reduce the amplitude of late indirect (I)-waves more so than early I-waves. Preferential activation of late I-waves can be achieved by using anterior-posterior (AP) stimulation. Threshold tracking is an alternative to conventional TMS, whereby a target motor evoked potential (MEP) amplitude is maintained in

the presence of the conditioning stimulus by adjusting the test stimulus intensity, thus removing the confound of MEP amplitude variability. We hypothesised that threshold tracking with AP stimulation may be a more sensitive technique to examine IHI compared to conventional methods. Fifteen neurologically healthy adults participated. Threshold tracking and conventional paired-pulse TMS protocols were used to examine short (10 ms) and long (40 ms) interval IHI in the non-dominant extensor carpi radialis (ECR) at rest and during voluntary activation of the contralateral ECR. Motor evoked potentials were recorded for PA, AP and lateromedial (LM) induced currents. Early and late I-wave recruitment was determined from MEP onset latency difference between PA-LM and AP-LM respectively. Threshold tracking short-interval IHI was greater with AP induced current than PA induced current ($P = 0.042$) and greater during contralateral activation compared to rest ($P = 0.022$). There were no differences between rest and contralateral activation, or between PA and AP induced current for short- or long-interval IHI using conventional paired-pulse TMS. The efficacy of late I-wave recruitment was associated with short-interval IHI assessed with AP induced current during contralateral activation (Threshold tracking: $r = -0.61$, $P = 0.025$; Conventional: $r = -0.65$, $P = 0.012$). Threshold tracking appears more sensitive than conventional paired-pulse TMS for assessing IHI, and may offer advantages for studying interhemispheric transfer.

Disclosures: R.A. Mooney: None. **J. Cirillo:** None. **W.D. Byblow:** None.

Poster

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Program#/Poster#: 061.19/DD35

Topic: E.04. Voluntary Movements

Title: Chronic stroke differentially alters distinct sensorimotor integration pathways

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Abstract: Somatosensory information is essential to inform motor output and allow for successful interaction with the environment. The neurophysiological process through which this occurs is termed sensorimotor integration. Sensorimotor integration can occur through two related, yet distinct neuroanatomical pathways. Information arising from proprioceptive related sensory receptors, such as muscle spindles, can ascend directly to the primary motor cortex (M1). Alternatively, information arising from the activation of other somatosensory fibres in the periphery, such as from cutaneous stimulation, initially reaches the primary somatosensory cortex (S1) before being relayed to M1 (Jones and Porter, 1980). Despite being behaviourally

relevant, sensorimotor integration has not been well studied in individuals with chronic stroke. The objective of the current work was to determine the influence of chronic stroke on sensorimotor integration. Fifteen individuals with chronic stroke and twelve older healthy controls participated. Sensorimotor integration was quantified by pairing median nerve stimulation or muscle belly vibration with single and paired-pulse transcranial magnetic stimulation (TMS). Short-latency afferent inhibition, afferent facilitation, and long-latency afferent inhibition were not different in individuals with chronic stroke, as compared to healthy older controls. In contrast, vibration had less of a facilitatory effect on motor-evoked potential amplitude ($p=0.05$) and there was a trend towards a reduced impact of vibration on intracortical facilitation ($p=0.07$) in individuals with chronic stroke as compared to healthy older individuals. Taken together, these results suggest that the more direct pathway of afferent information into M1 is altered in individuals with chronic stroke, whereas the pathway from S1 to M1 remains similar to controls.

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Poster

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Topic: E.04. Voluntary Movements

Support: NIH EB018783

W911NF-14-1-0440

Title: Neural correlates of sensory and motor delays explain temporal variance in simple reaction time experiments

Authors: *S. E. PARASKEVOPOULOU[1], W. G. COON[2], P. BRUNNER[1], K. J. MILLER[3], G. SCHALK[1]
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Abstract: Reaction time experiments are designed to study how the brain processes information to translate a sensory stimulus into a resulting behavior. Variations in reaction time are well documented, can be as large as the reaction time itself, and can be well modeled during experiments with varying task difficulty (e.g., using drift-diffusion models). Previous studies have had much less success in describing the delays in the sensory and motor systems observed

during tasks of the same complexity. These sensory and motor delays can add up to 100s of ms, which is substantially larger than what can be explained by synaptic or transduction latency variation. In our study, we use human electrocorticographic (ECoG) activity to quantify sensory and motor delays, construct a spatio-temporal model of successive processing stages, and link the temporal and physiological properties of this model to reaction times. Twelve patients with intractable epilepsy were temporally implanted with ECoG electrode grids. They participated in four different reaction time experiments involving different sensory stimuli. In all cases, they were instructed to push a button once the stimulus was detected. We applied the method described in (Coon and Schalk, 2016) to identify the ECoG locations with task-related activity in population-level, and to detect the onset time of cortical activity in individual trials. We then applied a novel functional connectivity algorithm to estimate the cortical progression of activation. The sum of the single-trial latencies between the corresponding cortical locations was significantly related to reaction time in all subjects, and explained up to 20% of its variance. Furthermore, we propose three physiological phenomena that underlie these variations in reaction time: 1) variations in perceived stimulus intensity; 2) variations in inhibitory modulation by alpha oscillations; and 3) bottom-up influences of sub-threshold activation in lower-level areas. Individually and together, these phenomena accounted for 2, 6, 13, and 18 percent of the delays at each location. The results of this work contribute to our understanding of the neural basis for variations in reaction time, and provide a conceptual framework for new research on this topic.

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Poster

061. Cortical Planning and Execution: Human Neurophysiology

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Topic: E.04. Voluntary Movements

Support: EC ECSEL-2015-1-RIA-692470

Spanish MINECO DPI2014-58431-C4-1-R

Title: Changes in cortical excitability after a BMI intervention using FES in a coordinated functional task

Authors: *J. L. PONS, A. MARTINEZ-EXPOSITO, I. DE ORBE, F. RESQUIN, L. J. BARRIOS, J. IBAÑEZ
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Abstract: Previous studies have demonstrated the possibility of increasing the cortico-spinal excitability using associative treatments where cortical states related to motor preparation are linked with peripheral afferent stimulation. In these studies simple types of proprioceptive feedback were used. It remains unclear whether the generalization of these associative facilitation paradigms using BMI and distributed afferent stimulation can increase cortical excitability in functional tasks. We test here changes in cortical excitability after an intervention with a BMI triggering FES. In this case, motor intentions are decoded from the cortical activity to causally deliver feedback. We present preliminary results of our research. The general hypothesis was that a distributed increase in cortical excitability could be obtained in areas targeting the muscles involved in the intervention task and receiving FES.
A BMI analysed the changes in the power of the motor cortical rhythms and the changes in the amplitude of slow potentials of the EEG. Based on this information the estimated probability of motor intention was in turn converted to trigger the FES currents on the muscles involved in the intervention task. Cortical excitability was assessed using TMS over the motor cortex representing four lower limb muscles by recording the MEPs. This assessment was applied Pre-, Post- and 30 minutes after the intervention with the BMI-FES platform. A 3-way repeated measures ANOVA was applied for the Muscle-Time-Intensity factors, and the post-hoc analyses were applied using Bonferroni´s Post-hoc correction. A Two-Way repeated measures ANOVA was applied in order to test Time-Intensity factors. The statistical significance was set at *0.05*. The 3-way ANOVA showed a significant main effect (Time) with an effect size of ^{2} = 58.2%. The Tibialis Anterior MEP amplitudes showed significant changes in the main effect (Time), with an effect size of ^{2} = 44%. Post-hoc pairwise comparisons showed significant differences between MEP measurements right before and after the intervention.
Results indicate that the proposed intervention leads to an increase in the cortical excitability in the muscles studied. The induced changes are not sustained (no longer significant 30 min. after the intervention), probably due to the short duration of the intervention. Future research will investigate on possible long-lasting effects after multiple sessions and on the spinal role in the observed change

Disclosures: J.L. Pons: None. **A. Martinez-Exposito:** None. **I. de Orbe:** None. **F. Resquin:** None. **L.J. Barrios:** None. **J. Ibañez:** None.

Poster

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Topic: E.04. Voluntary Movements

Title: Corticospinal inhibition during response preparation is abnormal in Parkinson's disease

Authors: *I. GREENHOUSE, R. B. IVRY
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Abstract: Transcranial magnetic stimulation (TMS) studies have shown that corticospinal (CS) excitability is inhibited during the preparation of responses. Whether this inhibition reflects the contributions of cortical and/or subcortical mechanisms is uncertain. Classic models of response preparation suggest the basal ganglia facilitate movement initiation by transiently inhibiting motor system output before a selected action can be released. Idiopathic Parkinson's disease (PD) is a movement disorder that disrupts basal ganglia function and results in impaired movement initiation. Here, we used TMS to measure CS excitability during the preparation of finger responses in a group of PD patients (n=13) on their typical medication. We hypothesized that preparatory inhibition would be abnormal in PD. At present, we compared the PD patients to a group of young healthy controls (n=27) with plans to test matched controls in the future. Participants performed a choice version of a delayed response task. On each trial of the task, a left or right index finger response was cued. After a 900 ms preparatory delay period, an imperative stimulus signaled the execution of the cued response. TMS was administered over right primary motor cortex 800 ms into the preparatory period, and motor evoked potentials (MEPs) were recorded using electromyography of the left first dorsal interosseous muscle. Reductions in MEP amplitude measured during the preparatory delay relative to MEPs measured during the inter-trial baseline served as an index of preparatory inhibition. The PD and control groups did not differ in baseline MEP amplitudes ($p = 0.57$). Healthy controls exhibited marked preparatory inhibition when the left index finger was selected ($t(26) = 10.6$, $p < 0.0001$) or non-selected ($t(26) = 4.9$, $p < 0.0001$). In contrast, PD patients did not exhibit inhibition when the left index finger was selected or non-selected (p's > 0.56). Moreover, the control group showed significantly greater inhibition than the PD group when the left index finger was selected ($t(38) = 4.0$, $p < 0.0001$) and non-selected ($t(38) = 2.9$, $p < 0.001$). These results suggest preparatory inhibition is dramatically decreased in PD, implicating a subcortical basal ganglia mechanism that influences CS excitability during response preparation.

Disclosures: I. Greenhouse: None. **R.B. Ivry:** None.

Poster

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Program#/Poster#: 061.23/EE3

Topic: E.04. Voluntary Movements

Title: Performance-driven modulations of beta cortical oscillations during sustained visuo-motor tracking

Authors: *M. PEREIRA[1], C. HOY[2], A. SOBOLEWSKI[1,4], J. LIN[3], R. T. KNIGHT[2], J. D. R. MILLÁN[1]
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Abstract: In producing precise behavior, our brain needs to constantly monitor the consequences of the actions it generates in order to correct for erroneous actions. Electrophysiological correlates of such a monitoring system have been repeatedly found in the medial frontal cortex. However they have been mostly investigated in tasks using single, well-defined erroneous events. Conversely, much of human behavior is a seemingly continuous and not easily parsed operation. In this work, we investigate electrophysiological correlates of performance in a sustained visuo-motor task.
We recorded four epileptic patients with electrocorticographic (ECOG) strips or depth electrodes (local field potentials; LFP) in the medial wall, while they used a mouse cursor to follow a moving target. Hand kinematics showed periodic pulses or "sub-movements" occurring at an average frequency of 5 Hz. Such sub-movements are a well-known phenomenon occurring in precise, visually-guided tasks. We used the time course (phase) of these sub-movements to segment the ECOG and LFP signals.
We found that instantaneous performance was reflected in the modulation of beta band (15-30 Hz) activity around the onset of sub-movements. This modulation was most robust in the ipsilateral supplementary motor area (SMA) of all subjects. Concretely, sub-movements produced while the cursor was ahead of the target correlated with an increase of beta amplitude. Lower SMA beta activation accompanied sub-movements effected with the cursor lagging behind the target. A control analysis showed that this beta modulation could not be explained by movement kinematics.
Based on the characteristics of the task, we attribute different behavioral values to the two situations. Cursor falling behind the target is more costly (erroneous) in terms of required corrective effort, than the cursor exceeding the target, i.e. situated at the target's future position. Consequently, we propose that the observed SMA beta modulations reflect the corresponding behavioral appraisal (performance monitoring). These beta modulations were most robust in the ipsilateral SMA, in accord with recent fMRI findings (Limanowski et al. 2017). Our findings, therefore, provide evidence that during continuous tasks requiring online evaluation (and correction) of end-effector position, the SMA engages in performance monitoring, intimately synchronized with sub-second motor output intermittencies, but not related to direct motor planning.
Limanowski J, Kirilina E, Blankenburg F. 2017. Neuronal correlates of continuous manual tracking under varying visual movement feedback in a virtual reality environment. NeuroImage. 146:81-89.

Disclosures: M. Pereira: None. **C. Hoy:** None. **A. Sobolewski:** None. **J. Lin:** None. **R.T. Knight:** None. **J.D.R. Millán:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: CRSNG

Title: The anticipation of reward and punishment differentially modulates oscillatory brain activity during reach planning: An electroencephalogram study

Authors: *F.-A. SAVOIE[1], R. HAMEL[2], A. LACROIX[2], F. THENAULT[2], K. WHITTINGSTALL[1], P.-M. BERNIER[2]
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Abstract: Studies have shown that sensorimotor brain regions are involved in encoding reward and punishment signals (Ramkumar et al. 2016; Iyer et al. 2010), presumably to help shape subsequent motor behavior. Little is known, however, on how this information affects neural activity related to movement preparation. In the present study, the purpose was to characterize how reward and punishment anticipation alters movement preparation. Twenty-two healthy participants took part in this EEG study. The experimental task consisted of reaching to visual targets with the right arm as precisely as possible. Visual feedback of the hand was only provided after reach completion to prevent online movement corrections. To investigate the effect of potential rewards and punishments on movement preparation, participants faced 4 different experimental conditions, presented in pseudo-random order: 1) Reward (R), where participants were rewarded with money (+5 cents) if they hit the target; 2) Punishment (Pu), in which missing the target resulted in a monetary loss (-5 cents); 3) Mixed (M), where participants were rewarded if they hit the target (+5 cents) but punished if they missed (-5 cents) and; 4) Neutral (N), in which target hits and misses were not rewarded nor punished. The condition was pre-cued 2 s prior to movement onset, providing a temporal window through which EEG activity relating to movement preparation could be investigated and compared across conditions. Power spectral density significantly differed in the theta frequency range (3 - 8 Hz), as well as in a broad beta spectrum of frequencies (10 - 30 Hz) at parietal and parieto-occipital electrodes bilaterally. Specifically, the prospect of being punished (Pu and M) was associated with a significant decrease in theta power throughout the movement preparation period as compared to conditions that did not involve punishment (R and N, $P \leq 0.01$), although R also showed significantly less theta power than N ($P \leq 0.01$). In the beta-band, the prospect of receiving a reward (R and M) was associated with a significant decrease in beta power during the first half of movement preparation compared to the non-rewarded conditions (Pu and N, $P \leq 0.01$). During

the same period, beta power in Pu was also significantly lower than in N ($P \leq 0.01$). The fact that rewards and punishments preferentially alter neural responses within different frequency spectrums (i.e. beta and theta frequencies, respectively) suggests that the observed differences in oscillatory activity are not a mere reflection of attentional modulations. Rather, these effects may reflect how the possible outcomes of actions shape neural activity related to movement preparation.

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Poster

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Canada Graduate Scholarships-Master's

Title: Motor cortical inhibitory and facilitatory circuit interactions in older adults

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Abstract: Short interval intracortical inhibition (SICI), short interval intracortical facilitation (SICF), and short latency afferent inhibition (SAI) are motor cortical circuits elicited by transcranial magnetic stimulation (TMS) that assess $GABA_A$ergic, glutamatergic, and cholinergic functions, respectively. These circuits interact with each other, and their interactions can be tested using triple-pulse TMS paradigms, which elicit one circuit in the presence of another. Here, we sought to determine what effects these circuits have on one another in older adults because the interactions between these circuits have yet to be examined in this age group. Ten right-handed participants (4 males; age range: 53-76 years) were studied. Surface electromyography measured target muscle (right first dorsal interosseous) motor evoked potentials generated by TMS of the left motor cortex. SICI was tested at an interstimulus interval (ISI) of 2 ms and SICF at an ISI of 1.5 ms. The interactions between SICI and SICF were evaluated by comparing SICF alone to SICF in the presence of SICI and by comparing SICI alone to SICI in the presence of SICF. The conduction time from median nerve stimulation to the

sensory cortex was determined for each participant with the latency of the N20 somatosensory evoked potential. This latency plus 2 ms was used as the ISI for SAI as this interval produces maximal SAI. The interactions between SAI and SICI were evaluated by comparing SICI alone to SICI in the presence of SAI and by comparing SAI alone to SAI in the presence of SICI. SICI in the presence of SAI was disinhibited (*t*-test, $P = 0.03$) and SAI in the presence of SICI was disinhibited ($P = 0.03$). SICF in the presence of SICI was facilitated ($P = 0.001$) and SICI in the presence of SICF was disinhibited ($P = 0.007$). SICI alone correlated with SICI in the presence of SAI ($r(8) = 0.683$, $P = 0.03$). SICF alone correlated with SICF in the presence of SICI ($r(8) = 0.719$, $P = 0.0167$). SICI alone correlated with SICI in the presence of SICF ($r(8) = 0.812$, $P = 0.0027$). These interactions are similar to previously reported findings in younger adults. Characterization of cortical interactions in older adults is necessary before studying such interactions in neurological diseases that are prevalent in older adults, such as Parkinson's disease.

Disclosures: J. Saravanamuttu: None. **N. Radhu:** None. **K. Udupa:** None. **C. Gunraj:** None. **R. Chen:** None.

Poster

062. Motor Planning in Humans

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 062.01/EE6

Topic: E.04. Voluntary Movements

Title: Cortical damage and disconnection independently contribute to stroke-induced deficits in limb-motor control and motor-task performance

Authors: *S. YAZDANI[1], G. YOURGANOV[2], J. FRIDRIKSSON[3], S. FRITZ[1], J. C. STEWART[4], T. M. HERTER[1]
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Abstract: Stroke is a major cause of neurological impairments of motor function. Understanding the brain regions and networks that underlie motor function can help guide post-stroke rehabilitation. Neuroimaging techniques that quantify stroke-induced damage to brain structures and disconnection of brain networks are powerful tools for examining the relationships between the brain and behavior. These techniques have advanced our understanding of the neural mechanisms that underlie perceptual, cognitive and language functions. However, studies of motor function have focused on damage and disconnection independently. Furthermore, most studies have focused on deficits in motor control without consideration for perceptual and cognitive contributions to motor performance. The purpose of this study was to examine if cortical damage and disconnection independently contribute to deficits in limb-motor control and

motor-task performance. We studied 50 subjects who survived a single, left hemispheric stroke at least six months before testing. We used a bilateral, object-hitting task on a KINARM robot to objectively measure deficits in limb-motor control (Hand-Speed Bias) and task performance (Target Hits). We used Magnetic Resonance Imaging to quantify damage (Lesion Volume) and Diffusion Tensor Imaging to quantify disconnection (Connectivity Bias) of five predetermined sensorimotor regions: Precentral Gyrus (PreCG), Middle Frontal Gyrus (MFG), Superior Frontal Gyrus (SFG), Postcentral Gyrus (PostCG), and Superior Parietal Gyrus (SPG). We observed significant, but moderate, relationships between damage and disconnection of these regions (r^2=0.31-0.52). Damage and disconnection of PreCG, MFG, SFG, and PostCG were significantly coupled to deficits in limb-motor control (damage: r^2=0.17-0.22; disconnection: r^2=0.16-0.27). In contrast, disconnection of all five regions exhibited a significant relationship with deficits in task performance (r^2=0.15-0.20), whereas only damage to PreCG and PostCG exhibited significant relationships with deficits in task performance (r^2=0.13-0.14). These results suggest that models for predicting chronic post-stroke deficits in motor function should incorporate cortical damage and disconnection with simple and complex motor tasks.

Disclosures: S. Yazdani: None. **G. Yourganov:** None. **J. Fridriksson:** None. **S. Fritz:** None. **J.C. Stewart:** None. **T.M. Herter:** None.

Poster

062. Motor Planning in Humans

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 062.02/EE7

Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant #05336

Title: Decoupling the eyes and arm: The neural correlates of looking and reaching in different spatial planes

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Abstract: "Standard" visually-guided reaching movements consist of a saccade and an arm movement made to the same location in space. However, many common tasks require us to use visual input presented in one location to guide an arm movement made in a different spatial plane (e.g. using a computer mouse). Deficits in the ability to use spatially dissociated visual information to guide arm movements are observed in association with dementia and concussion[1,2]. In the current study, we used fMRI to compare standard visually-guided reaching (i.e. coupled eye and arm movements to the same target) to a dissociated condition where

reaches were made on a different spatial plane than the guiding visual information. Specifically, in the dissociated condition, participants made hand movements on a horizontal plane to guide a cursor to targets presented on a vertical plane. A whole-brain iterative multivoxel pattern analysis (recursive feature elimination) was used to detect voxels containing reach category information during an instructed-delay epoch prior to movement initiation. Areas containing patterns of activity that consistently differentiated between motor planning in the standard and plane-dissociated tasks included the medial frontal gyrus, dorsal premotor, medial premotor, secondary somatosensory, and extrastriate regions of the cortex. These results provide insight into regions of the brain that may be at-risk in brain disorders that result in impairment of the ability to perform non-standard visually-guided arm movements. 1. Hawkins & Sergio, 2014, J.A.D. 42: 607-621. 2. Hurtubise et al., 2016, Concussion. 1(3): DOI: 10.2217/cnc-2016-0006

Disclosures: D.J. Gorbet: None. **L.E. Sergio:** None.

Poster

062. Motor Planning in Humans

Location: Halls A-C

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Program#/Poster#: 062.03/EE8

Topic: E.04. Voluntary Movements

Support: New Jersey Commission on Brain Injury Research (CBIR15MIG004)

Title: Investigating the corticomotor control of ankle plantarflexion in traumatic brain injury

Authors: *D. ALLEXANDRE, A. HOXHA, D. A. CUNNINGHAM, S. H. SALEH, E. SELVAN, G. H. YUE
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Abstract: Traumatic brain injury (TBI) can often result in gait and postural control impairment, which can lead to increasing risk of falls. To better understand this impairment, we used an isometric force control task to assess the corticomotor control of the ankle joints. While sitting, participant’s feet were attached to two pedals measuring plantarflexion forces which were displayed on the screen in real time. Participants were then asked to adjust their force to match a target line on the screen. For the first 10s, they had to maintain plantarflexion at 20% of their maximum voluntary contraction (MVC) (static condition). Then they had to dynamically adjust the force to follow the target line moving in a sinusoidal pattern between 15 and 25% MVC at 0.3HZ, the natural frequency of body sway, for another 10s (dynamic position). 16 trials for the left, right and both feet were performed. Force, muscle activities of the tibialis anterior (TA), gastrocnemius (GA) and soleus (SOL) and brain signals using a 64channels Brainvision EEG system were recorded. Independent component analysis and clustering were applied to the EEG data using the eeglab toolbox in order to isolate and study the dynamics of the specific brain

sources associated with the task. Up to date, 4 severe and 1 mild chronic TBI patients (55.8 +/- 4.4 yrs old) have been enrolled in the study. Several sources found in the premotor and motor brain regions, showed desynchronization in the beta (10-20Hz) and gamma bands (35-45Hz) typical of sensorimotor processing. This effect is larger during the dynamic vs the static condition. Future efforts will be aimed at comparing motor performance with age-matched healthy controls and elucidate specific neural markers of the deficit both in the dynamic vs static condition and when the task is performed with the left or right foot vs both feet. This information will be important to develop targeted and effective rehabilitation interventions to treat lower limb impairment in TBIs and improve balance and gait.

Disclosures: D. Allexandre: None. **A. Hoxha:** None. **D.A. Cunningham:** None. **S.H. Saleh:** None. **E. Selvan:** None. **G.H. Yue:** None.

Poster

062. Motor Planning in Humans

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 062.04/EE9

Topic: E.04. Voluntary Movements

Support: Daniel M. Soref Charitable Trust

Title: Cortical functional connectivity relates to changes in lower extremity mechanics due to increased cognitive load

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Abstract: Sports such as basketball and soccer involve a dynamic environment; requiring athletes to execute complex maneuvers in response to a multitude of external stimuli (e.g. teammates, opponents, the ball) without the opportunity to pre-select their movement. In addition, athletes frequently move while concurrently performing additional tasks associated with their sport (e.g. dribbling a ball, catching a pass). The neurocognitive demands associated with performing under these conditions are undoubtedly high. Thus, neurocognitive factors may strongly influence an athlete's risk of anterior cruciate ligament (ACL) injury. However, researchers and clinicians continue to have a limited understanding of the relations between neurocognitive functioning and ACL injury risk. Our purpose was to identify the cortical neurophysiological correlates to biomechanical variables that represent high-risk movement patterns. We hypothesized that the strength of functional connectivity between resting state networks would correlate with ground reaction forces that represent risky movement patterns during a landing task. Nine female participants completed a thorough biomechanical assessment

of landing kinetics and kinematics during either a pre-planned landing or an unplanned landing (requiring an increase in cognitive load). The differences in the ground reaction forces (GRF) for these two conditions were then calculated. Participants subsequently underwent resting state functional magnetic resonance scans. The default mode (DMN), sensorimotor (SMN), and the dorsal attention networks (DAN) were all identified using a seed-based approach in each participant. Correlations between the DMN and the other two networks were calculated. We divided the data into two groups based on ground reaction force differences, and calculated the mean and standard deviations of the correlations between the DMN and SMN, and between the DMN and DAN. Participants with the greatest differences in ground reaction forces (183N +/- 129N) had the weakest correlation between the DMN and the SMN (.004 +/- .133) or the DMN and the DAN (-0.014 +/- .35) compared to those with the smallest ground reaction forces (60N +/- 130N) (SMN .516 +/- .147; DAN .288+/- .234). Due to our small sample size, we also rank ordered the correlations of the DMN with the SMN and found that 4/5 participants with the largest GRF differences matched the four smallest correlations. These preliminary results provide insight into the neurophysiological basis for differences in athletes' risk for ACL injury, and expands our understanding of the role of neurocognitive factors on ACL injury risk.

Disclosures: W.E. Huddleston: None. **T.G. Almonroeder:** None.

Poster

062. Motor Planning in Humans

Location: Halls A-C

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Program#/Poster#: 062.05/EE10

Topic: E.04. Voluntary Movements

Support: NIH R01HD039343

Title: Brain activation during hand opening and closing tasks in able-bodied humans

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Abstract: There is some evidence indicating structural and functional differences in neuromuscular control system for extension and flexion movements of upper extremity. Brain activation during repetitive flexion/extension of the fingers has been studied using functional MRI (fMRI). However, the difference in brain activity during fingers extension versus flexion movements is still unknown. The goal of this study therefore was to use event-related high resolution fMRI to identify the whole brain functional activity during isolated hand opening and grasping tasks in able-bodied humans. To monitor and quantify finger activity, a MRI compatible kinematic glove and a pressure measurement bulb were used during fMRI of hand tasks to further investigate the relationship between brain activity and kinematics and kinetics of

the hand. Five able-bodied adults were recruited to participate in this study. During the fMRI tasks, subjects were instructed to either open, close, or rest their hand/fingers. Each fMRI run consisted 12 blocks, which included 6s of hand opening, 10s of rest, 6s of hand closing, and another 10s of rest. There were the total of 4 fMRI runs with short breaks between them. High resolution T1-weighted anatomical scans were obtained using a multi-shot gradient echo sequence. The functional echo-planar imaging scans had the following parameters: 72 axial slices, 2.0x2.0 mm in-plane resolution, 2.0 mm slices thickness, 620 volumes each run, TR/TE = 613/ 22 ms. Preprocessing and statistical analysis of the functional imaging data were performed using SPM12 software. Preprocessing steps included head motion and slice-timing correction, co-registration of the functional data to the T1-weighted scan, spatial normalization to MNI space, and smoothing with a 6-mm kernel. Voxel-wise statistical analysis was proceeded by using general linear model statistics to create the single subject contrasts with hand opening/closing and rest conditions entered as predictors. Second-level analysis (1 sample t-test) was used to identify the voxels with significant activity during the hand opening and closing tasks (p value <0.01). Finally, the correlation between brain activity and kinematics and kinetics of hand movement was tested. The results indicated differences in brain activation during hand opening versus closing tasks in humans. This paves the way to subsequent work on investigating the hand impairment in humans with movement disorder.

Disclosures: H. Karbasforoushan: None. **J.P.A. Dewald:** None.

Poster

062. Motor Planning in Humans

Location: Halls A-C

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Topic: E.04. Voluntary Movements

Support: FWO Vlaanderen G.0.622.08

FWO Vlaanderen G.0.593.09

KUL BOF-ZAP Startfinanciering (10/14)

Hercules II Funds

Title: Investigating shared representations of observed and executed actions using cross-modal fMRI decoding in rhesus monkeys

Authors: P. A. FIAVE, J. JASTORFF, *K. NELISSEN
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Abstract: *Background*: Neuroimaging techniques like multi-voxel pattern analyses (MVPA) and fMRI repetition suppression have been proposed as a means of inferring shared representations or common coding of observed and executed actions in the human brain (Oosterhof et al., 2013; Kilner et al., 2009). Contrary to monkey electrophysiology studies that suggest common coding in parietal and frontal cortices (Bonini, 2016), evidence from human studies also points to involvement of the lateral occipitotemporal (OT) cortex in representing one's own and others' actions (Oosterhof et al., 2010; Lingnau and Downing, 2015).
Methods: Here we employed fMRI decoding in rhesus monkeys performing or observing different actions. The focus of our study was twofold: 1) we examined whether monkey mirror neuron regions indeed show goal-specific cross-modal representations that can be retrieved by MVPA; 2) we investigated whether the monkey homologue of human OT complex represents observed and/or executed action goals and generalizes between visual and motor modalities. Monkeys either performed reach-and-grasp or reach-and-touch actions in the dark in the scanner or observed videos of human actors performing similar actions, while functional brain scans were acquired.
Results: Unimodal executed or observed actions goals could be decoded from mirror neuron regions, including rostral parietal, premotor and primary motor cortices, in addition to ventrolateral prefrontal cortex (VLPF). A monkey STS region functionally homologous to (part of) human OT also yielded significant distinct representations for different executed and observed action goals. Consistent with human results (Dinstein et al., 2008; Filimon et al., 2015), all previous regions also displayed highly distinguishable cross-modal multi-voxel patterns for similar executed or observed actions. Finally, while all mirror neuron regions yielded significant asymmetric (from visual to motor domain) goal-specific cross-modal decoding, the monkey OT homologue did not generalize between visual and motor modalities.
Conclusion: Our results suggest common coding of one's own and others' actions in the parieto-frontal mirror neuron regions, as well as in VLPF. The finding of asymmetric cross-modal goal-specific decoding is consistent with the proposed mapping of observed action goals onto the corresponding motor representations. Furthermore, while monkey STS should be regarded as an important stage for the visual analysis of body movements and actions (Nelissen et al., 2011; Giese and Rizzolatti, 2015), it does not seem to share the same functional characteristics as the parieto-frontal mirror neuron regions.

Disclosures: P.A. Fiave: None. **J. Jastorff:** None. **K. Nelissen:** None.

Poster

062. Motor Planning in Humans

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Topic: E.04. Voluntary Movements

Support: NIDCD Grant DC014664

American Heart Association Grant 15SDG24970011

USC Honors College SURF Grant

Title: Functional neural correlates of hand motor function differ based on level of motor severity in individuals post-stroke

Authors: *E. J. RIZOR[1], J. FRIDRIKSSON[2], C. RORDEN[3], L. BONILHA[4], G. YOURGANOV[3], D. M. PETERS[1], S. L. FRITZ[1], J. C. STEWART[1]
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Abstract: The neural correlates of motor function after stroke may differ based on motor deficit severity, supporting the need for investigation of brain-motor behavior relationships in functional subgroups. Resting-state functional connectivity (RsFC) may be a useful tool for exploring these relationships and can provide insight into brain function among individuals with a wide range of motor deficits. The objective of this study was to examine the relationship between RsFC and hand function after stroke, and whether this relationship differed based on level of motor severity. Sixty-three individuals with chronic, left-hemisphere stroke completed fMRI and three measures of hand function: Box and Blocks (BBT) test, Grip Strength, and Stroke Impact Scale Hand Domain. BBT performance was used to separate participants into three functional levels: Low (no blocks moved with paretic hand; N=13), Moderate (>0% but <90% of blocks moved with paretic versus non-paretic hand; N=27), and High (≥90% of blocks moved with paretic versus non-paretic hand; N=23). Resting-state fMRI was collected for 6 minutes from each individual with eyes closed (TR=1850 ms). Connectivity between motor regions (precentral, postcentral, posterior middle frontal, and posterior superior frontal gyri) within each hemisphere (ipsilesional, contralesional) and between homologous regions (interhemispheric) was extracted (Fisher Z) and correlated with hand function. Interhemispheric and ipsilesional connectivity significantly differed between groups ($p<0.05$), with the Low group showing decreased interhemispheric and increased ipsilesional connectivity compared to the High group. Mean interhemispheric connectivity significantly correlated with hand function (principal component of all three behavioral tests) across groups ($r=0.502$; $p<0.001$) and within the Moderate group ($r=0.428$; $p=0.026$). In contrast, in the Low group, hand function correlated with mean contralesional connectivity ($r=0.745$; $p=0.003$) and ipsilesional connectivity ($r=0.593$; $p=0.033$). No correlations were found in the High group. The brain network that supports hand function after stroke differed based on level of motor severity. Increased interhemispheric connectivity correlated with better hand function in individuals with moderate motor impairment, while increased intrahemispheric connectivity correlated with better hand function in individuals with more severe impairment. These findings may inform intervention approaches targeted at altering brain activation or connectivity and suggest optimal approaches for upper extremity rehabilitation may differ based on level of motor severity.

Disclosures: **E.J. Rizor:** None. **J. Fridriksson:** None. **C. Rorden:** None. **L. Bonilha:** None. **G. Yourganov:** None. **D.M. Peters:** None. **S.L. Fritz:** None. **J.C. Stewart:** None.

Poster

062. Motor Planning in Humans

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 062.08/EE13

Topic: E.04. Voluntary Movements

Support: NIH grant R01CA189665

Title: Coupling between parietal and motor cortex during motor imagery and execution tasks in post-chemotherapy cancer survivors

Authors: A. HOXHA[1], D. ALLEXANDRE[2], S. H. SALEH[2], E. SELAVAN[2], C. LEBOVIC[2], *G. H. YUE[3]
[1]Human Performance and Engin., [2]Kessler Fndn., West Orange, NJ; [3]Human Performance and Engin., Kessler Fndn. Res. Ctr., West Orange, NJ

Abstract: It has been shown that chemotherapy for cancer treatment is associated with side-effects such as fatigue, weakness and memory loss. The purpose of this study was to determine if conductivity among brain regions important for motor control is impaired in breast cancer survivors expereinced chemo treatment. Nine breast cancer survivors (52-69 years, right handed) participated in our study. Our experimental task involved 30 trials of mental imagery of maximal handgrip contractions (HGCs), 30 handgrip trials at 20% maximal voluntary contraction (MVC), and 30 trials handgrip at 20% MVC combined with mental imagery of maximal HGCs. EEG data was collected using a 64 channel actiCAP EEG system (Brain Products, München, Germany) and all data were processed using EEGLAB (MATLAB toolbox). Sources were calculated using the extended Infomax ICA algorithm, and their location was estimated on an MNI template. Source connectivity by fitting data into a Vieira-Morf linear model, and statistical estimates of the confidence intervals were computed using normalized Direct Transfer Functions. Sources were clustered into 4 active regions of the brain (Motor Cortex [M1], Supplementary Motor Area [MSA], Parietal Left [LP], Parietal Right [RP]) based on the ICA mapping, the source location and time-frequency activity. By modeling the directed time frequency interactions between sources of different regions, the results demonstrate a stronger connection between the LP and RP regions (compared to the other two tasks) in the alpha frequency band (8-12 Hz) during the Imagery Task, but this connectivity is disturbed during motor execution task or the combined task of motor imagery and execution. Strong connectivity was observed between M1 and LP and RP during the imagery and execution tasks in alpha (8-12 Hz) and beta (12-30Hz) bands, but the connectivity was modulated to higher frequencies during a the combined task. These data are in

the process of being compared to age- and gender-matched healthy controls to determine their physiological and clinical significance. Supported by NIH grant (R01CA189665)

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Poster

062. Motor Planning in Humans

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI Grant Number 15K21078

Title: EEG potential related to decision-making in direction-cue task by finger movements and saccadic eye movements

Authors: *A. FUNASE, Y. FUKUSHIMA, I. TAKUMI
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Abstract: [Purpose] We have been studying EEG signals related to the decision making on voluntary movements in the point of temporal patterns of brain activity. In this research, we perform the experiments using by the Direction-Cue and the Go-Cue. We can distinguish between the brain activity of decision-making related to direction of movements and the brain activity of connecting between the direction-cue and movements and the brain activity of preparation on movements. [Experiments] In this research, we perform the direction-cue task by finger movements and saccadic eye movements. Experimental order in the direction-cue task is as following. 1) A subject watches a fixation point on a computer display. 2) After 4.5-6.0 [sec], a direction-cue is presented to a subject. 3) After 2.5-3.0 [sec], a go-cue is presented to a subject. 4) When the direction-cue was shown as the right-arrow on a computer display, a subject pushes a right-side bottom in finger movements and moves his/her eyes to a right-target in saccades. When the direction-cue was shown as the left-arrow, a subject pushes a left-side bottom in finger movements and moves his/her eyes to a left-target in saccades. This order is one trial flow. We perform 50 right trials and 50 left trials. We record the EEG signals during these tasks. We focus on the C3, C4, Cz, P3, P4, and Pz electrode. EEG signals are processed by the ensemble averaging. On-set of the ensemble averaging is at starting time of the direction-cue. [Results and Discussion] From results, we obtain two features in finger movements and two features in saccadic eye movements. In the direction-cue task in finger movements, all electrodes have a positive potential after 300[ms] in presenting a direction-cue and a C3, C4, and Cz electrode has a negative potential after 1500[ms] in a direction-cue. In saccadic eye movements, all electrodes have a positive potential after 300[ms] in presenting a direction-cue and P3, P4, and Pz has a

negative potential after 1500[ms] in a direction- cue. A positive potential after 300[ms] in presenting a direction-cue are related to the brain activity of connecting between the direction-cue and movements. A negative potential after 1500[ms] is related to the brain activity of preparation on movements.

Disclosures: A. Funase: None. **Y. Fukushima:** None. **I. Takumi:** None.

Poster

062. Motor Planning in Humans

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 062.10/EE15

Topic: E.04. Voluntary Movements

Support: ERC Starting Grant, Horizon 2020

Title: Spontaneous action initiation with temporal constraints on the response time: An MEEG study

Authors: *B. TROVÒ[1,2], Z. ISCAN[1], A. SCHURGER[1,3]
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Abstract: The Readiness Potential (RP) is a slowly increasing surface-negative cortical potential that precedes spontaneous voluntary movements. A recent interpretation provided by the Stochastic Decision Model (Schurger, 2012) suggests that this slow buildup could be the result of event-locked averaging of ongoing sub-threshold fluctuations in neural activity. According to the model, autocorrelated background activity plays an important role in the preparation of actions when the external imperative to act is weak or absent: slow fluctuations continuously drift randomly closer to or farther from the decision-threshold for initiating action in an integration- to-bound fashion where ‘noise’ in the brain is integrated over time. In particular, the model predicts that movement is more likely to happen at a 'crest' in these ongoing fluctuations, and less likely at a trough. In classical RP studies subjects are instructed that they have an unlimited amount of time in which to perform the movement. We developed a new experimental paradigm in order to investigate the effect of varying amounts of temporal freedom on the shape of the RP/RF(Readiness Field, for MEG recordings). We perform a variant of Libet's (1983) task in which subjects are asked to initiate a finger tap within a given time window on each trial. Participants are free to make the movement whenever they want as long as they do it before the time has elapsed. The time limit variable, signalled by an animated clock, will vary among blocks in a counterbalanced way across subjects. Our main prediction is that the movement-preceding activity in pre-motor areas of the frontal lobe will appear to begin earlier,

and be more prominent in the time-locked average, as the window of time within which the subject is allowed to move becomes longer. The temporal constraint is predicted to affect the Early but not the Late component of the RP/RF. We would like to investigate parametric variations of the shape of the Readiness Potential/Field under temporal uncertainty, to unveil the timing mechanisms behind the non-movement and the movement states in the brain. The state transition between inaction-action has only recently been explored and is showing to be fundamental to the development of asynchronous BCIs (the ones that only respond when the subject intends to act and not otherwise). Indeed, so far most of BCI research has operated on discerning the content (*what*) of subjects' intention without much focus on its temporal features (*when*). Implementing both the *what* and the *when* information in the realisation of more powerful and ecological BCIs is a long- term goal of our project.

Disclosures: B. Trovò: None. **Z. Iscan:** None. **A. Schurger:** None.

Poster

062. Motor Planning in Humans

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Topic: E.04. Voluntary Movements

Support: NIH Grant R01NS090677

NIH Grant T32NS007480

Title: Demand on accuracy of hand movements is associated with distinct neural activity in primary motor cortex

Authors: *D. A. BARANY[1], K. P. REVILL[2], A. CALIBAN[1], K. SATHIAN[1,3,2,4], C. M. BUETEFISCH[1,3]
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Abstract: Performance of unimanual movements is often associated with premotor (PM) and primary motor cortex (M1) activity ipsilateral to the moving hand, in addition to contralateral activity. The magnitude of this activity increases with the demand of the motor task. However, it is unclear how this demand-dependent increase in neural activity is related to the control of hand movements. We assessed movement kinematics and blood oxygenation level-dependent (BOLD) activity patterns, as measured by functional magnetic resonance imaging (fMRI) during unimanual performance of a task that varied in the demand on accuracy. Participants used an MRI-compatible joystick to move a small cursor into a target in one of four possible locations. Motor demand was manipulated by varying target size (small, medium, large, extra-large) across

blocks of four movement trials. EMG activity of the extensor carpi ulnaris muscle was used to verify absence of movement of the non-moving hand. Movement accuracy increased, and movement time decreased, with increasing target size. In contrast, reaction time and the initial angular error of the movement did not scale with target size, suggesting that the employed task reflects demand on movement execution, but not preparation. Univariate analyses of the BOLD signal showed greater activation for smaller targets in both contralateral and ipsilateral PM and M1. We applied representational similarity analysis to the BOLD data to assess how neural patterns vary with changes in task demand. Preliminary evidence showed distinct activity patterns for movements of varying demand in both contralateral and ipsilateral M1, such that patterns during small movement blocks were most similar to the medium blocks and least similar to the extra-large target blocks. The similarity patterns were better explained by models based on the kinematic parameters of movement execution than movement preparation. These results suggest that demand on accuracy of a motor task is associated with neuronal activity patterns within M1 that are more closely related to movement execution than to planning.

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Poster

062. Motor Planning in Humans

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 062.12/EE17

Topic: E.04. Voluntary Movements

Support: Academy of Finland, grant No. 273971

Academy of Finland, grant No. 274086

Title: Association of aerobic fitness, physical activity and motor skills with basal ganglia volume in adolescents' brain

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Abstract: Introduction: Physical exercise and activity have been shown to improve cognitive and brain health. However, majority of such studies have focused on older adults and less is known about how physical activity affects the adolescent brain. In the current study we examined the relationships between basal ganglia structures, physical activity, aerobic fitness,

and motor skills in adolescents.
Methods: The brains of adolescents (41 females; age range 12.7-16.2 yrs) were scanned using magnetic resonance imaging (MRI). Aerobic fitness was measured with 20-m shuttle run test (*n* = 53), moderate to vigorous physical activity levels were determined using waist-worn accelerometers (*n* = 48), and motor skills were evaluated with throw and catch test (*n* = 55). MRI Images were acquired using a 3 T whole body scanner (Skyra, Siemens Healthcare) equipped with a 32-channel receive head coil (Siemens), and body transmit. T1-weighted structural images were acquired using an MPRAGE pulse sequence at 1-mm isotropic resolution; FreeSurfer (v. 5.3.0) was used for morphometric analysis of the basal ganglia.
Results: Correlation analysis showed statistically significant ($p<.05$) association between higher aerobic fitness and higher volume of globus pallidus. However, no correlation was found between aerobic fitness and the volume of caudate nucleus or putamen. Also, moderate to vigorous physical activity levels and motor skills did not correlate with basal ganglia volumes.
Conclusions: These results suggest that aerobic fitness correlates with basal ganglia in adolescents. This is in line with earlier studies showing that basal ganglia have a role in multiple aspects of movement production and our results support these findings. Interestingly, we found no association between the motor skill measurement (throw and catch test) and basal ganglia volume. Our results also imply that all moderate to vigorous physical activity as such may not influence basal ganglia volumes in youths. It could be that the intensity and frequency of physical activity has to be sufficiently high to improve aerobic fitness to cause detectable changes in basal ganglia volume. The current study provides evidence that aerobic fitness level may benefit certain important basal ganglia structures in the adolescents' brain.

Disclosures: I. Ruotsalainen: None. **V. Renvall:** None. **R. Pasanen:** None. **H.J. Syväoja:** None. **T. Tammelin:** None. **T. Parviainen:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: EU grant ERC-Advanced 320708

NIH Grant R01MH111417

Title: Mapping the human homunculus with receptive field analysis

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Abstract: Human sensorimotor cortex is somatotopically organized (Penfield and Boldrey, 1937). Despite the somatotopic distribution of body part representations, M1 and S1 neurons have also been reported to have overlapping receptive fields, which likely reflects the inter-relatedness of different body parts. Using fMRI, receptive fields of neuronal populations can be estimated by a Gaussian function (Dumoulin and Wandell, 2008). The current study shows that the population Receptive Field (pRF) approach can be applied to motor actions along the whole body, resulting in an approximately complete somatatotopy. Additionally, the receptive field sizes allow for the investigation of motor function integration.
During a 7T fMRI session, 4 healthy participants carried out a motor task involving the movement of 18 different body parts ranging from the toes to the trunk, to the arm and hand, and several facial movements. The participant moved each cued body part to an instructed position, which was followed by a movement in the opposite direction 1 second later. The fMRI results were fitted to a Gaussian function using a least square minimization algorithm. The Gaussian function estimates the preferred body part for each point on a reconstructed surface of the brain as well the receptive field size (σ), corresponding the level of response to other body parts.
We found a clear somatotopy of all investigated body movements in sensorimotor cortex (Pearson correlation of body part representation and cortical location R=.91), in accordance with the classical textbook homunculus. The receptive field sizes did not show a similar organization, but were dependent on body part type. Based on visual inspection of receptive field size, 3 different body movement types could be identified: the lower part of the body, the arm and hand, and the face. Each type displayed different receptive field sizes (R=.92) with the hand and arm showing the largest and the face showing the smallest receptive field size (σ=9.8 and σ=6.4 respectively).
The current study shows that the homunculus can be successfully mapped with fMRI on sensorimotor cortex within a single scan session. Additionally, the pRF analysis estimates receptive field sizes for each mapped body part. Current results show that the cortical hand area exhibits the largest receptive fields, which is likely caused by high levels of integration of specific hand and finger movements.
Dumoulin SO, Wandell B a (2008) Population receptive field estimates in human visual cortex. Neuroimage 39:647–660
Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389–443.

Disclosures: W. Schellekens: None. **N. Petridou:** None. **N.F. Ramsey:** None.

Poster

062. Motor Planning in Humans

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Topic: E.05. Brain-Machine Interface

Support: NSF award 1539068

NSF award 1430833

Title: Focal source localization of movement-related potentials with tripolar electroencephalography in realistic head models

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Abstract: Knowing where sources of activity are located in the brain can help with diagnosis. Locating the sources of electroencephalography (EEG) signals acquired on the scalp, the inverse problem, is an ill-posed problem since there are an infinite number of source configurations that can result in a particular potential distribution on the head surface. Therefore, additional constraints to the source space must be used to find a unique solution. Equivalent current dipole methods utilize a discrete source space in which a small number of dipoles are assumed to generate the given surface potential. Distributed source methods constrain the source space to a larger number of dipoles distributed either on the cortical surface or within the brain. Both methods have their advantages, but discrete source spaces yield an overdetermined solution while the solutions of distributed source methods are underdetermined. In the present study, the increased spatial resolution of tri-polar EEG [1] (tEEG) improved the focality of the underdetermined results found in distributed source localization methods with respect to movement related potentials (MRPs). Subjects (n=4) were concurrently recorded with both EEG and tri-polar concentric ring electrodes (TCREs) during a self-paced button press task. Subjects were instructed to press the button with the right thumb at a pace of 1 press every 2 to 3 seconds. Recording was stopped by the experimenter after 350 presses. Electrodes were placed on 16 of the standard 10-20 locations, excluding A1, A2, F7, F8, and T4. Surface potentials related to right thumb flexion were filtered with a low-pass filter (40 Hz cutoff) and segmented into epochs. Epochs containing artifacts were removed with a peak-to-peak threshold, and remaining epochs were averaged per subject. The subsequent average MRPs were localized using distributed source methods on the ICBM152 head model derived from a non-linear average of MRI scans of the 152 subjects in the MNI152 database. Using the open-source data analysis application Brainstorm, a linear L2-minimum norm estimates algorithm was used to localize sources to a source space constrained normal to the cortical surface.Localization results obtained from tEEG appear to be much more focal when compared to those of EEG. Thus, the underdetermined nature of distributed source localization methods is decreased when used with tEEG, alleviating this drawback and producing a more accurate representation of the MRP source signal. References: [1] Besio WG. et al."Tri-polar Concentric Ring Electrode Development for Laplacian," *IEEE TBME.* 2006.

Disclosures: C. Toole: None. **R. Bartels:** A. Employment/Salary (full or part-time):; CREmedical. **P. Steele:** A. Employment/Salary (full or part-time):; CREmedical. **J. DiCecco:** None. **W.G. Besio:** None.

Poster

062. Motor Planning in Humans

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Title: Integration of force and movement representation in proprioceptive area 2 of primary somatosensory cortex

Authors: *R. H. CHOWDHURY[1], B. M. LONDON[2], J. SOMBECK[1], C. VERSTEEG[1], T. TOMLINSON[2], L. E. MILLER[2,3,4,1]
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Abstract: Sometimes called the “hidden, sixth sense”, proprioception, the sense of body state, is crucial for movement control, yet remains poorly understood. Like other senses, it integrates submodalities to create a unified sensation. The most important of these are the senses of position, movement, and force. However, the way these submodalities are integrated and encoded in the brain is unclear. In this project, we probe the nature of this integration in area 2 of the primary somatosensory cortex (S1).
The classic model of proprioception assumes a linear combination of kinematic and force responsiveness. Neurons in S1 are thought to respond in different combinations to hand position, hand movement in a particular direction, as well as to the direction of an external force acting on the hand. Here, we argue that the representation of limb state in S1 is not this simple. Actively generated movements and passive perturbations, despite having similar trajectories, have different representations in S1 that is evident at the neural population level. In the high-dimensional neural state space, we found active and passive movements to be linearly separable. Using simulation, we show that this separation of active and passive representations cannot be achieved with the simple linear combination of force and movement information, suggesting there is a nonlinear integration of force and movement information in the representation of proprioception before the signals reach S1
Broadly speaking, this integration has two main potential sources: neural computation and peripheral mechanics. While muscle spindles primarily respond to muscle length and Golgi tendon organs (GTOs) to force, spindles are also activated by isometric contraction, and GTOs respond to muscle stretch when the muscle is active. Hence, we investigated whether the

nonlinear combination may be partially due to convergence of sensor information and characteristics of sensors. We stimulated the afferents using vibration, a selective stimulus for spindles, and brief electrically-evoked twitches, designed to activate GTOs. We characterized the response of S1 neurons using both methods. Neurons responded to vibration and GTO stimulation at ~40 ms latency. We also used a combination of motion tracking and musculoskeletal modeling to estimate muscle lengths and forces during reaching with and without added external loads. We modeled the output of muscle spindles and GTOs during these behaviors. Using these two independent approaches, we attempted to assess how the periphery contributes to this complex integration of submodalities.

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Poster

062. Motor Planning in Humans

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Topic: E.06. Posture and Gait

Support: JSPS KAKENHI Grant Number 24650383

JSPS KAKENHI Grant Number 15H05362

Title: Next-generation volumetric musculoskeletal model for motor neuroscience

Authors: *M. HIRASHIMA
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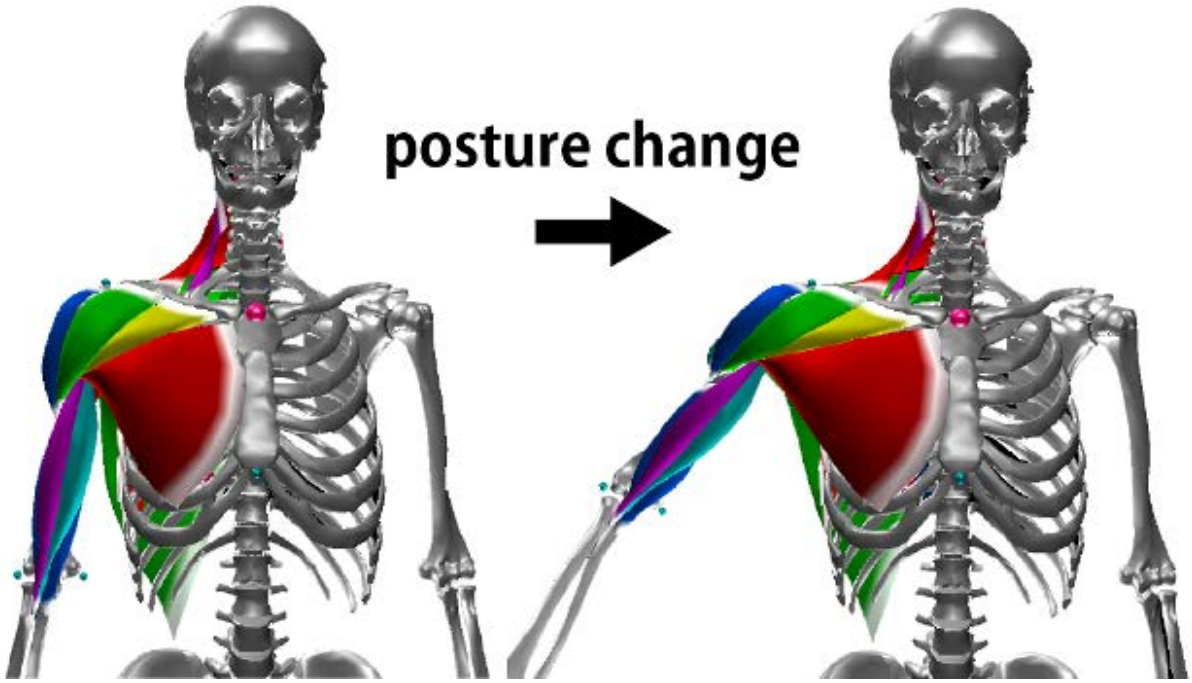
Abstract: One of the central questions in motor neuroscience is how the brain controls hundreds of muscles in our body. Although several hypotheses, such as muscle synergy or optimization, have been proposed, most of the previous studies have mainly focused only on the analyses of neural and muscle activation patterns, and paid less attention to the constraints arising from the mechanical or geometric properties of the musculoskeletal system. Especially, this tendency was prominent when three-dimensional (3D) movements were analyzed. One of the main reasons is that there are no good research tools that accurately express 3D muscle paths or their moment arms. In conventional human musculoskeletal models, the muscles are simplified as a straight line or a polygonal line without volume. Thus, it was basically difficult to accurately express muscle paths especially around the shoulder where many muscles interact with each other in a complex manner.
To fundamentally solve this problem, I have developed a new type of musculoskeletal model that considers muscle volumetric shape and its deformation arising from collisions with other

muscles and bones. In this model, the muscle shape was represented by a number of mass points located in a 3D grid. Although usually computational burden in simulating such a large degree of freedom is very high, I resolved this problem by computing the equations of the motions by adopting the GPU parallel computing method, which has developed rapidly in recent years. The advantage of the volumetric musculoskeletal model is that natural layered structure of the muscles even around the shoulder can be predicted by avoiding collisions among muscles and bones. This provides us with accurate moment arm information of the upper-extremity muscles, which is critically important for simulation and analysis of reaching movements. Furthermore, it can predict how the muscle moment arms are distributed or biased in hi-dimensional joint space. The model will promote our understanding of how the brain coordinates multiple muscles under the musculoskeletal constraints.



Disclosures: **M. Hirashima:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 3D Incorporated.

Poster

062. Motor Planning in Humans

Location: Halls A-C

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Program#/Poster#: 062.17/EE22

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI JP26120003

JSPS KAKENHI JP26120005

JSPS KAKENHI JP16H03219

Title: Age effects on smooth pursuit arm movement

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Abstract: Quantitative evaluation of human motor function is a key technology for evaluating effects of aging or treatments for patients with neurological disorders. In addition, it is ideal to make the evaluation available anywhere and anytime (e.g. at home). In our previous study, we developed a system for quantitative evaluation of wrist motor control using a simple tracking task with a manipulandum. Although the system was effective for evaluation of motor control, its custom-made device, e.g. manipulandum, was costly. Therefore it was difficult to use it at home to monitor daily or weekly changes.
We developed a new system for quantitative evaluation of motor function using a Kinect v2 sensor (Microsoft Inc.), which is available worldwide with low cost. The system consists of a Kinect v2 sensor, a laptop computer, and an LCD monitor. In our experiment, participants sat in front of the Kinect Sensor and asked to pursue a moving target presented on a display with a pointer whose position reflects position of the tip of his/her index finger. We analyzed the error, which is the distance between the pointer and the target position on the display, in real-time. The desired path of the target was not visible to the participants during the task, while they had some knowledge about the target motion due to preceding practice trials. A single session of the evaluation takes only about five minutes. We compared performance of tracking movements between 14 younger participants (21-24 years old), and 14 elder participants (49-81 years old). The error of the younger group was significantly smaller than that of the elder group. Among the elder group, those over 70 years old tended to show larger errors.
The present system could be further improved by connecting it to a cloud database system through internet (e.g., Microsoft Azure). Such a system will connect patients to medical doctors on-line and may make remote diagnosis into practice.

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Poster

063. Posture and Gait: Injury and Disease

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Topic: E.06. Posture and Gait

Support: NIH/NICHD R01HD082216

Title: Applying abrupt versus gradual pelvic assistance force to improve gait in individuals with post-stroke hemiparesis

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Abstract: An important goal of stroke rehabilitation is to improve gait patterns and function as gait dysfunction can increase the risk of falls and restrict functional mobility. Our previous study indicated that applying an assistance force in the mediolateral direction to the pelvis may promote weight shift toward the paretic leg and improve the symmetry of gait pattern. However, it is unclear whether a prolonged exposure to an assistive force will improve overground walking in individuals post stroke. The purpose of this study was to compare the effect of abrupt and gradual pelvic assistance force on overground walking in individuals with post-stroke. We hypothesized that applying an abrupt or gradual pelvic assistance force during treadmill walking would both improve over-ground spatiotemporal gait characteristics in individuals with post-stroke. Gradual pelvic assistance force would result in greater improvements compared to abrupt pelvic assistance force. Eleven subjects with chronic stroke participated in the study. A customized cable-driven robotic system was used to apply an abrupt or gradual assistance force to the pelvis toward the paretic leg. In the abrupt session, the magnitude of assistance force was constant at 9% of body weight during treadmill training. In the gradual session, the magnitude of assistance force was gradually increased to 9% of body weight during treadmill training. Each session consisted of 5 sections: 1-min baseline, 7-min treadmill training with pelvis assistance force, 1-min post-training (no force), 1-min standing break, and 5-min treadmill training with force. The order of the abrupt/gradual session was randomized across subjects. Spatiotemporal gait variables were evaluated using a 10-m instrumented mat before, after training, and 10 minutes after treadmill training. Overground walking speed improved after one session of treadmill walking with abrupt assistance force ($p < 0.01$), and with gradual assistance force, although this was not significant ($p = 0.05$). Step length of the paretic leg significantly increased after one session of training for both load conditions ($p = 0.03$), step length of the non-paretic leg significantly increased for the gradual load condition but was not significant for the abrupt load condition ($p = 0.08$). Stance time and single leg support time had no significant changes for both load conditions. Our results suggested that gait speed and step length of individuals post stroke could be improved by applying an assistant force to the pelvis toward the paretic side during treadmill walking, further studies with larger sample size are needed to determine whether abrupt vs. gradual force is more effective.

Disclosures: C. Hsu: None. **W. Dee:** None. **M. Wu:** None.

Poster

063. Posture and Gait: Injury and Disease

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Topic: E.06. Posture and Gait

Support: AHA Grant 11SDG7270001

Title: Dual-task gait speed while performing a visuospatial cognitive task is strongly related to gaze behavior during an obstacle crossing task for community-living individuals post-stroke

Authors: *L. A. ZUKOWSKI[1], J. A. FELD[2], A. DREWS[1], P. PLUMMER[1,2]
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Abstract: Walking around the house and community can be challenging for individuals post-stroke, requiring constant visuospatial planning to avoid tripping on small obstacles. Gaze behavior recorded during a visually-demanding walking task, like obstacle crossing, can provide important insight into visual information gathering but is not practical in clinical settings. Alternatively, walking performance, with or without the simultaneous performance of a visuospatial cognitive task (dual-task), can easily be collected in a lab or clinic, but its relationship to gaze behavior is currently unknown. The purpose of this study was to examine the relationship between gait speed during unobstructed walking with and without the additional performance of a visuospatial cognitive task and gaze behavior during obstructed walking. **METHODS:** Nine ambulatory, community-dwelling adults with stroke (mean±SD: 56.3±15.0 years old, 9.3±10.6 months post-stroke) participated. Gait speed (m/s) was recorded during single- and cognitive-motor dual-task unobstructed walking (walking while performing the clock task). Gaze behavior was recording during obstructed walking for both a low and high obstacle. Time from gait initiation to first fixation on the obstacle as a percentage of trial duration and percentage of time spent dwelling on the obstacle during the trial were calculated for each obstacle trial. Relationships between gait speed and gaze behavior were examined using Spearman's rho correlation coefficients. **RESULTS:** Dual-task walking speed was related to obstacle dwell time at both the low (rho=0.75, p=0.02) and high obstacle heights (rho=0.81, p=0.02) and to time to first obstacle fixation at the low (rho=-0.67, p=0.05) but not the high height. Single-task walking speed was positively related to obstacle dwell time at the high height (rho=0.88, p<0.01) but only approached a significant linear relationship at the low height (rho=0.62, p=0.08). Single-task walking speed was not related to time to first obstacle fixation at either obstacle height. **CONCLUSIONS:** Individuals post-stroke who walk faster while performing a visuospatial task (dual-task) tend to fixate sooner and for longer periods of time on anticipated obstacles in their path. These data suggest that dual-task walking ability is related to

how a person observes and gathers information about potential hazards in their environment. Individuals with slower dual-task gait speed tend to spend more time focusing on their more immediate walking path. Therefore, dual-task gait speed may be a useful indicator of how well a person will be able to navigate more complex environments after discharge from rehabilitation.

Disclosures: L.A. Zukowski: None. **J.A. Feld:** None. **A. Drews:** None. **P. Plummer:** None.

Poster

063. Posture and Gait: Injury and Disease

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Program#/Poster#: 063.03/EE25

Topic: E.06. Posture and Gait

Support: American Heart Association Award 16POST29610000

Title: The capacity to voluntarily modify asymmetry and reduce metabolic cost in people post-stroke depends on the direction of baseline asymmetry

Authors: *J. M. FINLEY, L. TREJO, N. SANCHEZ
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Abstract: Changes in the control of the lower extremities in people post-stroke often result in marked asymmetry and an increased metabolic cost during walking. Interventions that aim to reduce asymmetry rely on the presence of residual capacity to modify step lengths. However, this capacity may depend on the underlying impairments that influence the direction of asymmetry. Individuals who take short paretic steps may have deficits in both paretic limb advancement and paretic propulsion while individuals who take long paretic steps may have deficits in propulsion only. Here, we determine the degree to which the direction of step length asymmetry (SLA) impacts the capacity to restore symmetry and influences metabolic cost. We used visual feedback of foot placement to modify SLA during walking in a sample of 20 people post-stroke. The locations of markers placed on the greater trochanters and lateral malleoli were collected using optical motion capture, and the fore-aft distance between lateral malleoli markers was used to measure step length. Participants were tested under two conditions: 1) BASELINE, where we measured their natural SLA, and 2) FBK, where we provided visual feedback to aid them in increasing the length of the short step. Metabolic cost was measured using expired gas analyses. Linear models were used to determine 1) whether the magnitude and direction of participants' baseline SLA influenced their capacity to restore symmetry and 2) whether reductions in asymmetry reduced metabolic cost. Within our sample, we observed both positive and negative step length asymmetries ranging from 19% of stride length for those with longer paretic steps to 33% of stride length for those with longer non-paretic steps. The reduction in SLA during FBK was positively associated with baseline SLA magnitude ($p<0.001$) and the effects of this

association were larger in individuals with long paretic steps (interaction between SLA magnitude and SLA direction, p=0.002). During the FBK condition, metabolic cost was reduced for individuals who initially took long paretic steps, but was increased for people with short paretic steps (interaction between SLA direction and change in asymmetry, p = 0.042). Our results show that the ability to reduce asymmetry using visual feedback and the effects on metabolic cost depend on the direction of asymmetry: participants who take long paretic steps have a greater capacity to reduce asymmetry and are more likely to see an associated reduction in metabolic cost. Thus, reducing asymmetry may not be a uniformly effective approach to minimize the energetic cost of walking post-stroke.

Disclosures: J.M. Finley: None. **L. Trejo:** None. **N. Sanchez:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.04/EE26

Topic: E.06. Posture and Gait

Title: The effects of a 12-week exercise and cognitive intervention on gait, posture and Transcranial Magnetic Stimulation plasticity measures in individuals post stroke - an ongoing study

Authors: *J. GOMES-OSMAN[1], K. CAI[2], N. CASSIDY[2], J. RICE[3], D. CABRAL[4], S. ALDRAIWIESH[2], K. SARHADI[2]
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Abstract: Background: Cognitive impairments greatly contribute to decreased function and disability in individuals post-stroke. Improvements due to both, cognitive training and physical training interventions, are attributed to neuroplasticity. Single-pulse transcranial magnetic stimulation (TMS) interleaved with intermittent theta-burst stimulation (iTBS) allows for a non-invasive assessment of neuroplasticity. Our objective was to compare the effects of a 12-week exercise program to a combined program of exercise and cognitive training on measures of brain plasticity, gait and postural control in individuals post-stroke. **Methods**: All 8 participants fulfilled the following criteria: diagnosis of ischemic or hemorrhagic stroke, Modified Rankin Score of <4, sedentary prior to stroke, ability to walk ≥10 meters with or without assistance, and no absolute contraindications to receiving TMS. Subjects were randomized to receive either combined aerobic and resistance training (CARET, 45-60 minutes at 60-70% of HR max initially), (n=2); or CARET and a computer-based cognitive training (CTI, 30 minutes),(n=5). Both interventions were performed 3x/week for 12 weeks. Brain plasticity and gait function were

assessed at baseline and post intervention. **Outcomes**: Brain plasticity was assessed by comparing the amplitude of motor evoked potentials (MEPs) from single TMS pulses prior to (T0) and following iTBS (T10). For the gait and postural control assessment, individuals were fitted with a sensor-based gait analysis system (Mobility Lab; APDM, Inc), and performed the following tests: the Timed-Up and Go (TUG), TUG with dual-task (TUG-DT), and static standing balance (eyes open, eyes closed, and dual-task). **Results:** At a group level, all participants demonstrated improved dual-task time (mean=-4.1s, p=0.02) and peak velocity (mean=28.5m/s, p=0.054). In addition, there were within-group differences. The CARET+CTI group demonstrated an improvement in peak velocity (mean=41.5m/s, p=0.02) and the CARET only group demonstrated improved dual-task time (mean=-3.3s, p=0.03) and decreased double-support time (mean=-2.1s, p=0.005). Brain plasticity with TMS remained stable between assessments, and no differences were found. **Conclusion**: The results of this preliminary trial suggest that exercise delivered in isolation and combined with cognitive training may be useful in improving gait and postural control in persons post-stroke. The potential of TMS plasticity warrants further investigation.

Disclosures: J. Gomes-Osman: None. **K. Cai:** None. **N. Cassidy:** None. **J. Rice:** None. **D. Cabral:** None. **S. Aldraiwiesh:** None. **K. Sarhadi:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.05/EE27

Topic: E.06. Posture and Gait

Title: Stand-alone application of transcranial direct current stimulation: Does it speed up gait initiation in people after stroke?

Authors: *M. J. COPPENS[1,2], P. HERMANS[1,2], J. NONNEKES[1,2], A. C. H. GEURTS[1,2], V. WEERDESTEYN[1,2]
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Abstract: Chronic stroke patients have lower gait initiation speed than healthy controls[1]. As transcranial direct current stimulation (tDCS) has been reported to improve hand motor control in people with stroke[2], we aimed to study whether tDCS would also have a beneficial effect on gait initiation. For patients, we hypothesized that ipsilesional anodal tDCS (a-tDCS) would enhance cortical excitability of the affected hemisphere, whereas contralesional cathodal tDCS (c-tDCS) would decrease interhemispheric inhibition of the affected hemisphere, both improving leg motor output.We included 9 chronic supratentorial stroke patients, 10 healthy age-matched controls, and 10 healthy young adults. Participants completed three sessions on separate days

(one week apart), receiving 15 min of anodal, cathodal or sham stimulation (2mA) over the primary motor cortex in an order balanced across participants. For healthy controls, side of stimulation was balanced between hemispheres. After stimulation, participants were instructed to initiate gait with their preferred leg as fast as possible in response to a visual cue (12 trials). We determined median tibialis anterior (TA), rectus femoris (RF), anticipatory postural adjustments (APA) and step onset latencies. As the data were not normally distributed, nonparametric statistics were applied.No differences were found in the effects of stimulation between stroke patients and healthy controls. For TA, c-tDCS showed a trend towards delayed motor responses compared to sham stimulation (158 vs. 151ms, p=0.050), which was not found for RF (161 vs. 160ms), APA (202 vs. 203ms) or step (510 vs. 513ms) onsets. a-tDCS did not influence onset times compared to sham stimulation (*TA*: 150 vs. 151ms; *RF*: 156 vs. 160ms; *APA*: 207 vs. 203ms; *step*: 511 vs. 513 ms). Six out of 9 stroke patients stepped with the 'stimulated' leg (directly by a-tDCS or indirectly by c-tDCS). In controls, this was the case for 9 out of 20 participants. We did not observe differences in the effect of tDCS between subjects who stepped with the 'stimulated' leg and those who did not.Contrary to our expectations, we found no evidence of any tDCS-induced benefits in reaction times of gait initiation. In all groups, c-tDCS even tended to delay the very first response in TA, which effect was no longer present in subsequent components of gait initiation. The present results do not support the use of stand-alone tDCS for achieving improvements in gait initiation in people with stroke. [1]Tokuno and Eng. Gait & Posture, 2006 24(4):424-8 [2]O'Shea et al. NeuroImage, 2014 (85):924-933

Disclosures: M.J. Coppens: None. **P. Hermans:** None. **J. Nonnekes:** None. **A.C.H. Geurts:** None. **V. Weerdesteyn:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.06/EE28

Topic: E.06. Posture and Gait

Support: Heart and Stroke Foundation of Ontario

Title: Do physical performance measures of posture and gait predict quality of life and community reintegration after stroke?

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Abstract: Mobility is instrumental to community participation for stroke survivors. It is a common assumption that recovery of physical performance abilities in posture and gait will

result in better community reintegration and health-related quality of life for individuals recovering from stroke. This study assessed 55 individuals post-stroke within a month after discharge (baseline) from inpatient rehabilitation and 6 months later using the following measures: SF-36 (Physical Component Summary (PCS) and Mental Component Summary (MCS)), Subjective Index of Physical and Social Outcome (SIPSO; total, physical integration, and social integration scores), Timed Up and Go (TUG), Community Balance and Mobility Scale (CB&M), Berg Balance Scale (BBS), Six Minute Walk (6MW), Isokinetic Torque defined by the sum of the ankle, knee and hip extensors average torque on the paretic and non-paretic legs and Postural Control measured by the center of pressure (COP) area on the paretic and non-paretic sides during quiet stance and arm raise perturbations of the non-paretic arm. Separate stepwise linear regressions were performed with quality of life (SF-36 PCS and MCS) and community reintegration (SIPSO, total, physical and social integration scores) as the dependent variables to determine if baseline physical performance measures predicted the dependent variables at 6 months. SF36 PCS at 6 months was significantly predicted by the baseline BBS and 6MW distance but no other independent variables. The SF-36 MCS was not predicted by any of the physical performance measures. Community reintegration (SIPSO total and social integration scores) at 6 months were significantly predicted the baseline TUG time, whereas the SIPSO physical integration score was significantly predicted by the baseline BBS and 6MW distance. In summary, participants who performed better on several physical performance functional measures upon discharge from inpatient stroke rehabilitation had better quality of life (physical component) and community reintegration at 6 months post-discharge. There were fewer instances of impairment-based measures (i.e. strength or postural control) influencing quality of life or community reintegration post stroke.

Disclosures: S. Garland: None. **T.D. Ivanova:** None. **D. Bryant:** None. **B. Brouwer:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.07/EE29

Topic: E.06. Posture and Gait

Title: Immediate effect of mental singing while walking on gait disturbance in hemiplegic stroke patients

Authors: *S. LEE, H. SEOK, J. KIM
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Abstract: Introduction
Mental singing while walking is simple to perform, requires no special tools and could be utilized anytime and anyplace. It was introduced to have potentials for improving the gait of

individuals with Parkinson's disease. But there is no study investigating the effect of mental singing on gait in post-stroke patients. The aim of this study was to investigate the immediate therapeutic effect of mental singing while walking on gait in post-stroke hemiplegic patients.

Method

Eligible post-stroke hemiplegic patients were prospectively enrolled in this study. Inclusion criteria were as follows: 1) patients who were diagnosed with hemiplegia due to stroke on magnetic resonance imaging and computed tomography (onset time of less than 12 months) and had no previous history of strokes; 2) patients who were able to walk more than 10 meters with or without gait aids; 3) Korean version of the Mini-Mental State Examination (K-MMSE) score of 24 or higher. Each patient underwent structured music therapy session which consist of 7 consecutive tasks, and were trained to sing in their mind (mental singing) while walking. Before and after training session, gait ability was assessed by measuring 10-Meter Walk Test (10MWT), Timed Up and Go test (TUG), gait velocity, cadence and stride length.

Results

Twenty patients were enrolled and completed interventions. After mental singing while walking, there was significant improvement in 10MWT ($P = 0.02$) and TUG test ($P = 0.06$). As for gait characteristics, there was also significant improvement in cadence ($P < .001$), stride length ($P < .001$) and velocity ($P < .002$).

Conclusion

Mental singing while walking has immediate positive effects on improving the functional clinical outcomes and gait abilities of hemiplegic stroke patients.

Disclosures: S. Lee: None. **H. Seok:** None. **J. Kim:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.08/FF1

Topic: E.06. Posture and Gait

Support: NIH Grant R00 HD073240

Title: Influences of a single session task-specific perturbation-based training on compensatory stepping response can contribute to reduced risk of falling in stroke survivors

Authors: *M. NEVISIPOUR[1], M. GRABINER[2], C. HONEYCUTT[1]
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Abstract: Stroke survivors are at major risk of falling. Falls lead to severe injuries and increased morbidity. Current exercise-based training programs have shown to be unsuccessful in reducing

falls in stroke survivors. Task-specific perturbation-based training which exposes subjects to numerous balance perturbations, and elicits compensatory stepping response, has shown to reduce falls in older adults and individuals with Parkinson's disease. The purpose of this study was to evaluate the effects of a single session task-specific training on compensatory stepping response of stroke survivors following balance perturbations. Secondary, the effects of training were evaluated in Fallers and Non-fallers separately.
Sixteen subjects with unilateral stroke were exposed to treadmill perturbations which required forward stepping to avoid falling. Subjects stood on the treadmill while fitted in a harness and perturbations were delivered unexpectedly in three different intensities (small, medium and large) before and after training which consisted of 15 moderate-intensity perturbations. Trunk kinematics, step kinematics and center of mass (COM) stability measures were evaluated at the first step initiation and foot strike.
The ability to limit trunk motion was improved after training at small and medium perturbations. Falls in older adults and stroke survivors have been previously found to be characterized by larger trunk flexion angle and velocity following a balance perturbation. Thus, our results suggest that task-specific training can reduce falling risk by enhancing the stepping response of stroke survivors. However, training had no significant impact on their stepping response and falling outcome in large perturbations. We suggest future work should evaluate the effects of multiple sessions of task-specific training including perturbations with varying intensities.
Successful stepping responses of Fallers after training resembled Non-fallers' responses prior to training. Moreover, Fallers were more influenced by the training. Further research is required to investigate whether speed and capacity of learning is different between Fallers and Non-fallers. More specifically, future work should evaluate if falling at pre-training can impact the effectiveness of task-specific training.
The main outcome of this study was that a single session of task-specific training could significantly modify trunk kinematics. These results are consistent with our previous results in older adults that led to reduced falls. Thus, we suggest that an extended version of task-specific training can reduce risk of falling in stroke survivors.

Disclosures: **M. Nevisipour:** None. **M. Grabiner:** None. **C. Honeycutt:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.09/FF2

Topic: E.06. Posture and Gait

Support: FAPESP 2015/25376-9

FAPESP 2013/02322-5

FAPESP 2010/15218-3

Title: Locomotor adaptation in individuals with stroke using body weight support on a treadmill versus over the ground

Authors: *A. M. BARELA[1], G. L. GAMA[1], D. V. RUSSO, Júnior[1], D. S. SANTANA[1], M. L. CELESTINO[1], J. A. BARELA[1,2]
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Abstract: We have the flexibility for choosing different locomotor patterns according to the environmental contexts, physical condition and behavioural goals. In this way, we should make adjustments of a well-established motor task that occurs in response to a new stimulus or perturbation. This process is defined as motor adaptation, and it is an important capability for learning a new walking pattern. Among different populations with walking impairment, individuals with stroke seek to reestablish walking and partial body weight support (BWS) systems have been used as a training strategy for gait rehabilitation poststroke. In this study we investigated the adaptability of the locomotor pattern in individuals with stroke using BWS system on a treadmill versus over the ground. Six individuals with chronic stroke were assessed in two sessions with one week apart, walking with a BWS system on a treadmill in one session and over the ground in the other session. Two inertial sensors were placed on each foot of the participant for the whole session to register spatial-temporal parameters. In each session, participants were asked to walk at self-selected comfortable speed along a 10m walkway back and forth five times, and mean walking speed was calculated. Afterwards, they walked with the assistance of the BWS system at approximately 80% of calculated speed. Each of the two sessions consists of 3 periods: baseline period (2-min walking with 0% of BWS), adaptation period (10-min walking with 20% of BWS), and deadaptation period (1-min walking with 0% of BWS). Average step length and stance period duration of paretic and nonparetic limbs were calculated during baseline period, first and last 3 strides of adaptation period (early and late adaptation, respectively), and first and last 3 strides of deadaptation period (early and late deadaptation, respectively). Individuals with stroke presented longer step length in the paretic compared to the nonparetic limb and over the ground compared to the treadmill. On both surfaces, they decreased step length from baseline to early adaptation, maintained it in the late adaptation and increased it in early and late deadaptation, although in late deadaptation, step length was longer compared to baseline. They presented longer stance duration for the paretic limb on treadmill compared to over the ground, on the treadmill both paretic and nonparetic limbs presented similar stance duration as over the ground, non-paretic limb presented longer stance duration compared to the paretic limb. These results suggest that individuals with stroke can gradually adjust step length to the new stimulus, however, but not the stance duration.

Disclosures: **A.M. Barela:** None. **G.L. Gama:** None. **D.V. Russo:** None. **D.S. Santana:** None. **M.L. Celestino:** None. **J.A. Barela:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.10/FF3

Topic: E.06. Posture and Gait

Support: VA RR&D O1435-P

VA RR&D F7823S

University of Florida Graduate School Fellowship

Title: Corticospinal efficacy to the medial gastrocnemius predicts gait function following stroke

Authors: *C. PATTEN[1,3], V. L. LITTLE[3], C. L. BANKS[2,3], T. E. MCGUIRK[3]
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Abstract: Ankle plantarflexion (PF) is critical for producing forward propulsion, momentum, and limb advancement during the swing phase of gait. Gait deficits, including PF power generation, are prominent and well recognized following stroke. Currently only 50% of stroke survivors respond to gait therapies; the underlying mechanism of therapeutic response is poorly understood. Here we measured motor evoked responses (MEPs) in response to single-pulse TMS delivered during both isometric and dynamic ankle PF contractions in 34 adults: (13 Control (61.7(8.5) yrs, 7 male), 21 post-Stroke (64.9(8.9) yrs, 82(58) months, LE FMA 25.8(7.2), 18 male)) to test the hypothesis that gait function following stroke is associated with corticospinal efficacy to the plantarflexors. Participants were seated, positioned with the knee at 20- 30º flexion. Single-pulse TMS was delivered over the ipsilesional (target) hemisphere using a custom Fig-8 coil (70mm diameter/wing) at 120% of resting motor threshold during isometric and dynamic PF contractions to assess corticomotor excitability and modulation during dynamic efforts. Stimulation location was determined by online evaluation of MEPs to maximize responses in the paretic (target) leg plantarflexors (SOL, MG). Neuronavigation (BrainSight2) tracked and maintained coil location. Participants generated PF torque between 10-20% of maximum voluntary contraction for 1 second which then triggered stimulations to occur while the ankle was held at (isometric), or moving through (dynamic), neutral position. SOL, MG, and tibialis anterior (TA) MEPs were manually identified and ensemble averaged (~10 repetitions per condition); MEP_{area} was normalized to background EMG of the respective muscle. Ankle power (A2), our primary outcome for gait function, was derived from inverse dynamics using data obtained during a separate instrumented gait analysis study. MG MEP_{area} during dynamic PF correlated with A2 ($R = .463$, $p = .008$) across both Control and Stroke groups. TA MEP_{area} was not associated with gait function in either group. Stepwise regression using K-fold cross-

validation (5 iterations) identified parameters predicting A2 magnitude in both Stroke (A2= .54011 +.0312 $MG_{dynamic}$ -.0031 Chronicity, R^2 = .675) and Control (A2 = 2.48 - .007 $MG_{dynamic}$, R^2 = .21) groups confirming our hypothesis that efficacy of cortical drive to the plantarflexors during active movement predicts walking function following stroke. We anticipate that identification of individuals with residual corticomotor function to the plantarflexors retain the intrinsic capacity for walking recovery following stroke.

Disclosures: C. Patten: None. **V.L. Little:** None. **C.L. Banks:** None. **T.E. McGuirk:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.11/FF4

Topic: E.06. Posture and Gait

Support: Parkinson's Queensland Inc. PhD project grant 2013-2016

Title: Beta frequency corticomuscular coherence is reduced during walking in people with Parkinson's disease

Authors: *L. ROEDER[1], T. W. BOONSTRA[2], S. S. SMITH[3], I. B. STEWART[1], G. K. KERR[1]
[1]Inst. of Hlth. and Biomed. Innovation, Queensland Univ. of Technol., Kelvin Grove, Australia; [2]Black Dog Inst., Univ. of New South Wales, Sydney, Australia; [3]Univ. of Queensland, Brisbane, Australia

Abstract: *Objective:* Gait difficulties are a common symptom of Parkinson's disease (PD), even at early stages of the disease. Alterations in the structure and function of multiple cerebral regions, including basal ganglia and cortico-frontal networks, may contribute to gait disorders in PD. The role of the motor cortex and the corticospinal tract in Parkinsonian gait disorders is not well understood, which this study aimed to investigate.
Methods: Here we examined healthy young (n=22; 25±3 years), healthy older (n=24; 65±7), and people with early-stage PD on medication (n=20; 67±7). Participants performed overground and treadmill walking at a self-selected speed while electroencephalography (EEG) from bilateral sensorimotor cortices, electromyography (EMG) from tibialis anterior (TA) muscles (left/right), and temporal gait cycle events via foot switches were recorded. Time-dependent corticomuscular coherence (CMC) relative to heel strike was assessed pairwise between EEG from bilateral sensorimotor cortices and EMG from the contralateral TA muscle. A sub-group of PD participants (n=14) also completed experiments in an off medication state (overnight withdrawal).
Results: We found significant CMC at 13-21 Hz (beta) during the double support phase of the gait cycle for overground and treadmill walking in all groups ($p<0.003$). People with PD showed

significantly reduced beta CMC compared to healthy young (p=0.002) but not compared to healthy older controls (p=0.2). There was a trend towards reduced beta CMC in healthy older compared to healthy young people, although the effect was not statistically significant (p=0.052). In the PD sub-group who participated both on and off medication, beta CMC was not significantly different between on and off medication states (p=0.9).
Conclusions: Beta CMC during walking was found to be reduced in people with PD, and unaffected by levodopa medication. We propose that these results indicate deficiencies in afferent and/or efferent corticospinal processes during walking in people with early-stage PD. Moreover, we speculate that these deficiencies may be related to non-dopaminergic pathologies. This research advances the current understanding of neural control of human gait and how it is affected in PD. Ultimately, it will improve treatment options for neurodegenerative disorders such as PD and assist the development of neuro-prosthetic devices.

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Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.12/FF5

Topic: E.06. Posture and Gait

Support: NIA (R01AG006457, Horak)

Department of Veterans Affairs (5I01RX001075, Horak)

Title: Cortical contributions to gait in people with Parkinson's Disease and Frontal Gait Disorder

Authors: *P. CARLSON-KUHTA[1], M. L. SINGER[1], O. MIRANDA DOMINGUEZ[2], I. ARPAN[1], M. N. AHMED[2], D. A. FAIR[2], F. B. HORAK[1,3], L. A. KING[1]
[1]Neurol., [2]Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [3]VA Portland Hlth. Care Syst., Portland, OR

Abstract: *Background:* Gait deficits in Parkinson’s disease (PD) are the consequence of the loss of dopaminergic input to the basal ganglia, however, recent studies have suggested an importance of frontal cortex input to compensate for gait deficits. Frontal Gait Disorder (FGD) causes gait abnormalities similar to PD but with more cognitive impairment. The purpose of this study was to use a dual-task (DT) paradigm to explore the impact of cognition on gait for people with PD and FGD. We hypothesized that compared to healthy control subjects 1) PD subjects would have a greater DT cost and FGD subjects would have less DT cost, and 2) PD subjects would have increased functional connectivity between subcortical locomotion centers and frontal

cortex regions, whereas FGD subjects will have reduced functional connectivity between these regions.
Methods: Participants included 10 subjects per group: PD, FGD, and Healthy Control (HC). Subjects completed 1) a seated cognitive task (recite alternating alphabet letters), 2) walking trial, and 3) walking trial with cognitive task. Gait parameters were measured with Opal inertial sensors (on feet, lumbar, sternum, and wrists). Gait metrics were calculated from Mobility Lab (APDM). Dual Task Cost (DTC): [(Dual task – Single task)/Single task] x 100 and Cohens d effect size were calculated. A subgroup of subjects had resting state MRI (rsMRI) to compare connectivity between locomotor regions (e.g., pedunculopontine nucleus, PPN) and cortical regions (e.g., anterior SMA).
Results: People with FGD worse gait (slower gait speed, longer double support time and slower turn velocity) and fewer cognitive task responses, compared to PD and HC groups. People with FGD had less DTC than PD and HC, with PD and HC groups both having large effect sizes for DTC (> 0.8 Cohen's d for gait speed and double support time). No differences in DTC in number of correct answers to cognitive task during single (seated) or dual (walking task) were found for any group. Preliminary analysis of rsMRI shows a trend of FGD (-0.065 ± 0.11) and PD (-0.002 ± 0.01) having no connectivity from PPN to anterior SMA regions, but an inhibitory connection in HC (-0.21 ± 0.16).
Conclusion: Our results suggest that people with PD rely on cognitive compensation for gait deficits, whereas FGD do not. All groups had relative preservation of alphabet task during DT, suggesting the prioritization of cognition over gait. Overall we found a trend of inhibitory connectivity between PPN and SMA for HC, and no trend in PD and FGD. We are adding more subjects and continuing imaging analysis to explore potential functional connectivity differences between FGD and PD.

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Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.13/FF6

Topic: E.06. Posture and Gait

Support: NIH Grant RO1 NS088679

MnDRIVE Brain conditions

NIH Grant NINDS 1P50NS098573

Title: Evaluating postural instability using treadmill perturbation in Parkinson's disease

Authors: *C. LU[1], E. L. TWEDELL[1], K. H. LOUIE[2], S. L. AMUNDSEN HUFFMASTER[1], M. N. PETRUCCI[1], C. D. MACKINNON[1], S. E. COOPER[1]
[1]Dept. of Neurol., [2]Biomed. Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: Postural instability (PI), as a symptom of Parkinson's disease (PD), is associated with increased risk of falls and decreased quality of life. Currently, there is no fully effective treatment for PI. The revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the generally accepted clinical measure for symptom severity in PD (Goetz et al., 2008) and PI is assessed in the MDS-UPDRS by item 3.12, the "pull test." Due to the difficulty of applying a correct and consistent postural perturbation (pull backwards by the shoulders), as well as the complicated examiner instructions this test is often performed improperly, even in clinical trials (Munhoz et al., 2004).
The purpose of this study was to examine whether a more consistent treadmill-induced horizontal perturbation of the support surface can provide a measure of postural instability as well as overall motor signs in people with PD.
Twenty PD patients (0 - 7 years from diagnosis; 19 - 54 MDS-UPDRS total motor scores off-medication state) and 6 control subjects of similar age participated in the study. Subjects stood on a stationary treadmill. Ten total trials were collected, 5 facing the rear of the treadmill (backward step required to recover balance) and 5 facing the front (forward steps required). After a verbal warning, followed by a variable interval, the treadmill was turned on for 0.65 sec (0.2 sec at 5 m/sec^2, 0.05 sec at 0 m/sec^2, then 0.4 sec at -2.5 m/sec^2). All subjects required at least 1 step to reach postural stability.
High definition video of the lower extremities was recorded at 60 Hz and inspected by a blinded rater using standard video-editing software to quantify reaction time, number of steps and step duration. We also collected center of pressure data from the treadmill’s integral forceplate and surface EMG from bilateral lower extremity muscles.
We present preliminary results validating metrics extracted from our data against UPDRS total motor score as a gold standard. We conclude that our treadmill perturbation is suitable for measuring long-term changes in Parkinsonian postural control and the response to intervention, when the standard UPDRS pull test is impractical or unreliable.

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Poster

063. Posture and Gait: Injury and Disease

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Program#/Poster#: 063.14/FF7

Topic: E.06. Posture and Gait

Support: NIH Grant 5R00HD078492

Title: Cortical correlates of sensory augmentation to alleviate freezing of gait

Authors: *M. MANCINI[1], G. BOOTH[1], L. A. KING[1], J. QUINN[2]
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Abstract: Background: Over 80% of patients with Parkinson's disease (PD) eventually develop freezing of gait (FoG), one of the most disabling symptoms which frequently occurs during tasks that require asymmetric balance control such as turning, or may be exacerbated under dual-task conditions, suggesting a dependency of gait and turning on cortical attention in freezers that may be due to loss of automaticity related to basal ganglia dysfunction. Recently, functional near infrared spectroscopy (fNIRS) has been used to measure changes in cortical oxygenated hemoglobin (HbO2) levels, and increased HbO2 levels are related to increased blood flow, which, in turn, reflects increased cortical activity. Here, we hypothesize that dual-task walking and turning will results in an increased activation of the frontal lobe and an even higher frontal lobe activation will precede FoG. In addition, we expect that closed loop vibrotactile biofeedback will be alleviate FoG by reducing the frontal, attention demands of gait.
Methods: Nine subjects with PD (MDS-UPDRS: 50±9, Age: 65±7) OFF medications and 5 healthy controls (Age: 63±7) participated in the study. Participants performed an objective assessment that consisted of performinging a set of motor tasks (turning and walking) at baseline and while using vibrotactile feedback. They wore 3 inertial sensors and a wireless portable, functional 8-channel fNIRS system (OctaMon, Artinis). After low-pass filtering with a cut-off frequency of 0.14Hz, HbO_2 concentrations will be calculated as sum of the 8-channel from both sides of the forehead. Relative changes in the concentrations of HbO_2 were obtained using the most proximal 20-s baseline (collected prior to command start walking for each task) where participants were asked to stand still.
Results: Prior to a turn, HbO_2 slightly increased by 0.023 ± 0.439 μM before FoG, and increased by an additional 0.361 ± 0.254 μM during the turns with FoG. In contrast, controls showed an opposite trend, HbO_2 largely increased by 0.231 ± 0.170 μM before a turn, and then decreased to 0.107 ± 0.312μM during the turn. The use of tactile biofeedback in PD seems to restore HbO_2 values closer to controls. In fact, prior to a turn, HbO_2 increased by 0.197 ± 0.560 μM before a turn, and increased by an additional 0.261 ± 0.172 μM during the turn.
Conclusion: These preliminary findings support the association between FoG and changes in

frontal lobe HbO_2. Increased activation in the frontal cortex during FoG highlights the connections between motor planning, information processing, and FoG. Also, the use of tactile biofeedback seems to be effective in decreasing FoG and frontal lobe HbO_2.

Disclosures: M. Mancini: None. **G. Booth:** None. **L.A. King:** None. **J. Quinn:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.15/FF8

Topic: E.06. Posture and Gait

Support: University of Wisconsin Foundation

Title: Frequency-dependent lower-limb coordination during standing is altered in Parkinson's disease

Authors: *W. BOEHM[1], K. GRUBEN, 53706[1], K. DOYLE-GREENE[2], L. WINTER[3]
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Abstract: Standing balance commonly appears compromised in persons with Parkinson's disease (PD), however, the mechanism of impairment is not well-understood. The complex contribution of motor and somatosensory deficits in the disease, as well as unilateral and axial symptoms, make characterization of impairment elusive. In particular, little is known about how PD alters the ankle, knee, and hip torque coordination that produces an appropriate ground-on-foot force (*F*) for retaining upright posture. In the sagittal plane, non-impaired individuals use a near-linear relation between the center-of-pressure (CP) of *F* and the ratio of horizontal to vertical components of *F*. The slope of that relation varies across frequency, with higher frequencies producing greater horizontal force, relative to CP displacement, that generally results in less-stabilizing *F* character. Across frequencies, PD showed higher horizontal force gain relative to CP displacement than non-impaired individuals, revealing a possible explanation for their balance impairment. This metric goes beyond typical CP analysis and may be useful to inform effective rehabilitation strategies, diagnose risk of falling, and document illness progression.

Disclosures: W. Boehm: None. **K. Gruben:** None. **K. Doyle-Greene:** None. **L. Winter:** None.

Poster

063. Posture and Gait: Injury and Disease

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Program#/Poster#: 063.16/FF9

Topic: E.06. Posture and Gait

Support: Once Upon A Time Foundation RGC0000001029

KU Investment Council Strategic Initiative Grant

National Institute of Health 1U54HD090216-01

Title: Postural control deficits in aging Fragile X mental retardation 1 (FMR1) gene premutation carriers

Authors: *Z. WANG[1,2,3], P. KHEMANI[4], M. W. MOSCONI[1,2,3]
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Abstract: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disorder. Penetrance of FXTAS increases with age and onset typically occurs after 50 years with a subsequent rapid progression of symptoms. Identification of sub-clinical indicators of disease progression may assist in development and implementation of disease modification therapies. We aimed to identify neurobehavioral phenotypes in aging FMR1 premutation carriers currently asymptomatic for FXTAS during both static and dynamic stances. 19 FMR1 premutation carriers and age-matched healthy controls completed tests of static and dynamic postural stances on a force platform. During static stance, participants were instructed to stand as still as possible with their feet shoulder-width apart. During dynamic stance trials, participants were instructed to continuously sway their body either anterior-posteriorly (AP) or medial-laterally (ML) at a comfortable speed and magnitude. Relative to controls, premutation carriers showed increased COP_{ML} standard deviation during static stance. During both dynamic postural sways, premutation carriers showed COP standard deviation reductions in target directions compared to healthy controls, whereas their COP standard deviation was elevated compared to controls in directions orthogonal to the target. Relative to controls, premutation carriers also showed increased COP_{ML} regularity for each postural condition. During both dynamic stances for which postural sway primarily involved uni-dimensional movement, controls showed a significant reduction in their mutual information (MI) compared to the static stance. Relative to static stance, premutation carriers showed an MI reduction during ML body sway but not during AP sway. We find new evidence that sub-clinical sensorimotor disturbances

affecting postural control are present in aging FMR1 premutation carriers who do not meet clinical diagnostic criteria for FXTAS. Our results suggest that postural control in FMR1 premutation carriers holds promise as a preclinical biomarker which could have a role in the development of effective neurotherapeutic strategies for FXTAS.

Disclosures: Z. Wang: None. **P. Khemani:** None. **M.W. Mosconi:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.17/FF10

Topic: E.06. Posture and Gait

Title: Relation between cognitive function, walking ability and strength for adults with autism spectrum disorder

Authors: *C. N. ARMITANO[1], T. KOZIKOWSKI[2], S. I. DEUTSCH[2], M. R. URBANO[2], S. NEUMANN[2], H. CARACCI[3], S. MORRISON[1]
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Abstract: Autism spectrum disorder (ASD) is a common neurodevelopmental disorder affecting 1 in 88 persons in the US. This disorder is characterized by patterns of repetitive behavior, interest or activities, along with divergences in social interaction and communication. In recent years, increased attention has been given to the motor deficits common in individuals with ASD, such as altered gait, clumsiness, toe walking, and catatonic-like motor behavior. Motor impairment may be intricately linked to social impairment in ASD, with motor limitations inhibiting early social development. The aim of the current study was to assess the differences in walking ability, hand grip strength, reaction time (RT), and balance control between a group of young adults with ASD (n=20, age 21.2$\pm$4.4 years) and healthy age-matched adults (n=20, aged 24.3$\pm$2.8 years). Gait was assessed while participants performed five trials at their preferred speed (PWS) and five subsequent trials performed as fast as possible. Each person's walking performance was assessed using a 20 ft GAITRite pressure sensitive walking surface. Balance was assessed using a force platform under the following conditions: 1) eyes open/firm surface, 2) eyes closed/firm surface, 3) eyes open/foam surface, and 4) eyes closed/foam surface. Simple reaction time was assessed for the hand and foot (15 trials each). Results demonstrated that, with regard to the balance measures, there was no differences between the ASD group and the controls. In contrast, the adults with ASD had significantly slower reaction times and decreased hand grip strength. Furthermore, the individuals with ASD had a significantly different gait pattern, characterized by decreased stride and step times, slower gait velocity's (at both preferred and faster walking paces) and decreased cadence. Overall, in addition to the decreased cognitive

processing speeds (i.e. RT), differences in motor function were evident for strength assessments and gait. However, the lack of any group differences in postural control during the static balance assessments may indicate that the motor deficits associated with this disorder are more commonly linked to dynamic movement performance and/or strength measures rather than balance alone. Together the findings indicate that though there may not be any differences in static balance tasks, these results confirm that persons with ASD exhibit a number of motor and cognitive declines in comparisons to healthy adults of a similar age.

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Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.18/FF11

Topic: E.06. Posture and Gait

Support: Wilson Research Foundation, Methodist Rehabilitation Center

Title: Postural strategies utilized by lower limb prosthesis users and controls while dual-tasking

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Abstract: Postural control can be disrupted due to multi-tasking or physical limitations resulting in the use of postural control strategies to meet the increased demand and maintain balance. Lower limb amputees have sensorimotor impairments known to impact postural control; yet, little is known about selection and adaptation of postural strategies in this population.
The objective of this study was to assess the use of postural control strategies, specifically the posture first (greater focus on balance) or posture second (less focus on balance) strategy, during dual-task standing in 13 below knee prosthesis users and 15 age/education-matched controls. The subjects placed each foot on a force plate and stood for 30 s under usual (hard surface/eyes open) and difficult (soft surface/eyes closed) conditions, first alone (single-task) and while concurrently performing a cognitive task (dual-task) without and then with instruction on cognitive prioritization. The outcome measures included path length, 95% sway area, and anterior-posterior (AP) and medial-lateral sway amplitudes.
During single-task standing, the two groups were not different except for greater AP amplitude in the difficult standing condition in the prosthesis users ($p=0.004$). During dual-task standing without instruction on prioritization, prosthesis users showed an increase in all sway outcomes regardless of standing condition ($p<0.03$), supporting the use of the posture second strategy.

Controls, however, showed a decrease in sway outcomes during the difficult dual-task standing condition ($p<0.02$), supporting the use of the posture first strategy. With cognitive task prioritization, sway was unchanged or reduced ($p<0.05$) in the prosthesis users, suggesting departure from the posture second strategy, whereas controls maintained the posture first strategy. Individual analysis revealed that greater postural demand in controls ($p<0.04$) and greater cognitive challenge in prosthesis users ($p<0.04$) led to both reduced sway and improved cognitive performance, suggesting cognitive-motor facilitation.
Prosthesis users and controls allow for greater sway while concurrently performing a cognitive task under less demanding postural condition (hard surface/eyes open), suggesting the posture second strategy when stability is not at risk. However, with increased challenge (postural in controls and cognitive in the prosthesis users), subjects may improve performance on both tasks. The overall results suggest dynamic capabilities of postural control systems and that activation of additional resources, rather than posture prioritization, is relied upon when faced with increased demands.

Disclosures: C.L. Howard: None. **B. Perry:** None. **J.W. Chow:** None. **C. Wallace:** None. **D.S. Stokic:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.19/FF12

Topic: E.06. Posture and Gait

Support: NIH R01 HD069769

Title: Segmental stabilizing strategies used by cerebral palsy with and without visual dependence during upright stance

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Abstract: In typically developing children (TY), segmental stabilization strategies emerge as they navigate through an environment with increasing balance challenges. This process may not occur in individuals with cerebral palsy (CP) as they lack the capability to pursue these challenges. We hypothesized that diminished sensory processing contributes to the impaired segmental stabilization strategies observed in ambulatory adults with CP. In the current study, we explored inter-segmental stabilizing strategies exhibited by 18 adults with TY and 22 adults with spastic CP during perturbations of the supporting surface and visual surround. Using a rod-and-frame test, 11 CPs tested visually dependent (VD) while all remaining subjects were visually

independent (VI). In a virtual environment, subjects stood on a platform that tilted rapidly in the toe-up direction by 3°, remained tilted over a period of 30s, and slowly returned to the neutral position over another period of 30s at 0.1°/s to diminish vestibular feedback. The surrounding visual scene was kept dark, stationary, or rotated pitch downward or upward. Sagittal plane orientation of head, shoulder, hip, and ankle was calculated. Angle-angle plots from adjacent segments were formed and fitted into ellipses. The ellipse area was then compared against visual scene conditions across 3 groups (TYVI, CPVI, CPVD) using repeated measure ANOVAs in 4 platform conditions (tilt, post-tilt, sustained tilt, return). Both CPVI and CPVD had significantly greater ellipse area during tilt and post-tilt than TYVI in all segmental pairs ($p<.01$). During tilt, CPVD adopted a hip stabilizing strategy producing movement variability in the trunk; TYVI and CPVI adopted an ankle strategy ($p<.01$). CPVD also showed a reduced ellipse area compared to CPVI during post-tilt, but was not able to fully stabilize during sustained tilt when the surrounding visual scene was moving ($p<.01$). During return, CPVI and CPVD adopted a hip stabilizing strategy producing movement variability in the trunk, while TYVI adopted an ankle strategy ($p<.01$). Our results suggest that diminished somatosensory signals and increased weighting of visual inputs produce prolonged instability following a postural disturbance and may contribute to decreased functional mobility in adults with cerebral palsy.

Disclosures: Y. Yu: None. **R.T. Lauer:** None. **C.A. Tucker:** None. **E.A. Keshner:** None.

Poster

063. Posture and Gait: Injury and Disease

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Program#/Poster#: 063.20/FF13

Topic: E.06. Posture and Gait

Support: American Diabetes Association Award 7-12-CT-49

Title: Older adults with Type 2 Diabetes classified as fallers have slower reactions, decreased strength, and impaired postural stability compared to non-fallers

Authors: *R. SIMMONS[1], S. COLBERG[2], S. MORRISON[3]
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Abstract: For older adults with type 2 diabetes (T2DM), a history of falling, general declines in strength, speed of reactions, diminished postural control, and the presence of neuropathy can be collectively viewed as mitigating factors for increased risk of falling. This study was designed to investigate the differences in lower limb strength, reaction time (RT), postural control and coordination for 81 older individuals with T2DM classified as either fallers or non-fallers. All persons were diagnosed with peripheral neuropathy. Determination of fall status was based upon self-reports of whether a person had fallen in the past year (i.e. faller) or not (i.e. non-faller). Of

this cohort, 21 persons were classified as fallers (age 67.5±6.0 years) while the remaining 61 persons did not report falling previously (age 67.1±4.6 years). No significant clinical differences were noted between the groups (Fallers: BMI 31.2±4.5, HbA1c 7.4±1.4, neuropathy score 10.8±5.1; Non-Fallers: BMI 32.2±5.8, HbA1c 8.2±2.2, neuropathy score 9.5±5.9). Balance was assessed using a force platform under the following conditions: 1) eyes open/firm surface, 2) eyes closed/firm surface, 3) eyes open/foam surface, and 4) eyes closed/foam surface, and 5) postural tracking (i.e., coordination) task. RT measures were assessed for the hand and foot. While the results revealed no differences between the groups with regards to the level of peripheral neuropathy, fallers exhibited a number of differences in the various physiological measures: significantly slower reactions for the hand and foot, decreased knee extension and flexion strength, and diminished proprioception. Additionally, fallers exhibited impaired balance during the more challenging tasks (i.e. eyes open/closed on the foam surface) characterized by increased postural sway in both the AP and ML directions (i.e., mean, SD, and range of COP motion). The diminished balance control was further reflected by a greater number of errors during the postural tracking task. In conclusion, the emergence of neuropathy, slower reactions, and diminished strength and balance control means that older persons with T2DM generally have a higher risk of falling. However, even within this population, persons with T2DM who have suffered a fall recently exhibit greater impairment in postural control. This finding illustrates that while the presence of neuropathy does affect motor function related to balance, it cannot solely account for differences in postural control between those with T2DM classified as fallers compared to non-fallers.

Disclosures: **R. Simmons:** None. **S. Colberg:** None. **S. Morrison:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.21/FF14

Topic: E.06. Posture and Gait

Support: Injury Biomechanics and Aging Lab, University of Waterloo

Frank Lab, University of Waterloo

Thank you to Amy Hackney, PhD.

Title: Acute anxiety may alter dynamic stability in healthy, young adults during dual-task conditions

Authors: *A. N. BICKNELL, A. C. LAING, J. S. FRANK
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Abstract: ***Objectives***: i) To investigate the effects of anxiety on dynamic stability during gait and visuospatial recall in a healthy, young adult population; and ii) to establish a comparative dataset for investigations with older adults.
Methods: 11 healthy, male and female young adult participants (mean(SD)= 20.6 (3.1) years old) were randomized into the control (n=5) or experimental-anxiety (n=6) group. All participants completed three tasks: i) Seated visuospatial task, ii) Walking at self-selected pace along a 7-metre pathway for 2-minutes, and iii) Dual-task (walking and visuospatial task). The experimental-anxiety group completed an anxiety-inducing task prior to each trial. Participants were outfitted in 6 inertial sensors (lumbar, trunk, wrists, shanks) to record 14 limb and trunk metrics using the APDM Mobility Lab inertial sensors. Anxiety levels were assessed using a self-report scale.
Results: Both groups reported comparable, low baseline anxiety (mean(SD) =1.2(1.3) out of 10). Increased anxiety was reported following each of the anxiety-inducing trials (3.9(2.1) out of 10, $p<0.05$). No significant difference in visuospatial performance was observed between the groups ($p=0.33$). Increased movement of the trunk in the frontal plane was observed in the anxiety group during the dual-task ($p=0.04$). Reduced arm swing range of motion ($p=0.009$) and longer turn durations ($p=0.04$) were observed during the dual-task within the anxiety group.
Conclusions: In healthy young adults, mild to moderate anxiety appears to influence dynamic stability and task performance. Healthy, young adults appear to have a tendency to prioritize a visuospatial task during dual-task conditions, at a cost to alterations in dynamic stability. The observed changes in balance control may increase the risk of falling under more challenging walking conditions and in populations with impaired gait and balance. Future research should determine whether similar changes are observed in older adults and populations with balance control challenges; and ii) whether their control strategies are sufficient to compensate for these potential changes in dynamic stability.

Disclosures: **A.N. Bicknell:** None. **A.C. Laing:** None. **J.S. Frank:** None.

Poster

063. Posture and Gait: Injury and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 063.22/FF15

Topic: E.06. Posture and Gait

Title: The effect of music on movement and anxiety

Authors: M. DUNN[1], J. L. JENSEN[1], D. GUPTA[1], J. BARTHOLOMEW[1], L. MAGUIRE[2], *L. D. ABRAHAM[1]
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Abstract: Previous research has described some interactive relationships among music, movement, and anxiety. While a few creative art therapy studies have supported the idea of positive effects on health, most of these results have not been systematically investigated or replicated. The purpose of this project was to explore methods of quantifying the effects of music on movement patterns as well as their interactive effects on levels of state anxiety. Using a 9-camera VICON motion capture system, kinematic measures were obtained when nine healthy young adult non-dancers completed a 30-second whole body movement task with and without music playing. These two conditions (music/silent) were tested on different days and the order was balanced across participants. From these data, heel strike time (during walking) and wrist pause times (during arm movements) were identified. The relative timing of these movement events was then studied and compared to the timing of the beats in the music condition. Physiological measurements (pulse rate and blood oxygenation) and a state-trait anxiety assessment were administered before and after practicing and performing the movement task during each session. All participants also completed a questionnaire after each session, describing their thoughts about their performance and their attention. Analysis of kinematic data focused on the following variables: variability of heel strike timing during stepping, variability of wrist inter-movement intervals, and synchronization of each movement event with the music beat (during the music condition). Interactions between these kinematic measures and the measures of anxiety across testing conditions were also examined. One subgroup of participants exhibited marked reduction in anxiety following the movement task, others did not. This subgroup was further analyzed to identify potential contributing factors. In addition, there did appear to be an interactive effect of the order in which the music conditions were tested, since the reductions in anxiety were usually during the participants' second testing session, regardless of testing condition. This practice effect also was found when the movement kinematics were examined for synchronization with the beat of the music. The effect of music was observed in addition to this practice effect, as some participants who had a larger anxiety reduction in the music condition than the silent condition showed lower movement variability in the music condition than the silent condition, regardless of testing order. These findings should inform future research examining interactions between movement and music as they affect participant anxiety.

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Poster

064. Posture and Gait: Healthy Development and Aging

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Program#/Poster#: 064.01/FF16

Topic: E.06. Posture and Gait

Support: Nasjonalforeningen for folkehelsen ProjectID 4882

Title: The Association of white matter integrity and gait speed during dual-tasking among community-dwelling elderly adults

Authors: *S. A. CASTRO-CHAVIRA[1], T. R. VANGBERG[2], M. M. GORECKA[1], O. VASYLENKO[1], K. WATERLOO[1], C. RODRÍGUEZ-ARANDA[1]
[1]Fac. of Hlth. Sciences, Dept. of Psychology, Univ. of Tromsø, Tromsø, Norway; [2]Dept. of Radiology and Nuclear Med., Univ. Hosp. North Norway, Tromsø, Norway

Abstract: Background: Changes occurring in gait and attention during normal aging increase the incidence of falls. To date, few studies have explored the role of white matter degeneration in normal aging with impaired gait during concomitant cognitive performance. Methods: To address this issue, measures of gait speed from two groups of healthy elderly adults performing walking baseline (BL) and a dual-task paradigm consisting of dichotic listening (DL) during over-ground walking were obtained. DL challenges gait by presenting different auditory stimuli to each ear in three conditions: unrestricted attention, or non-forced (NF) condition, where subjects decide which source of stimulus to attend; and forced attentional conditions, either forced right (FR) or forced left (FL), where subjects need to attend stimuli from right or left ear. Two age groups of right-handed elderly, 29 younger (M = 65.52, 59-70 years old) and 31 older (M = 75.87, 71-88 years old) were evaluated with the Optogait©-system. Means and coefficients of variation (CV) per condition were calculated. In addition, brain DTI images were acquired to assess white matter integrity using Tract-Based Spatial Statistics (TBSS). Results: During the dual task, the younger group presented faster average speed than the older group in the BL, FR, and FL conditions. No group differences existed in speed during the NF condition. Non-parametric permutation analysis using threshold-free cluster enhancement (P = 0.05) and the general linear model applied to the TBSS analysis were used. Comparison of white matter between groups showed larger FA values in the younger group in left callosal body, inferior longitudinal fasciculus, thalamic radiation and optic radiation. In addition, the association between gait speed and DTI indices demonstrated greater FA values in the younger group in two conditions: NF and FL. During the NF condition, FA correlated with average speed, while in the FL condition FA values correlated with speed CV. In both cases, the white matter tracts of interest were the corpus callosum, superior longitudinal fasciculus, and optic radiation from the left hemisphere. Conclusion: Results of the present study showed significant associations for the DL conditions with highest cognitive difficulty. Thus, in healthy elderly, faster gait velocity and higher variability of speed under demanding conditions depend on better integrity of left hemispheric white matter tracts.

Disclosures: **S.A. Castro-Chavira:** None. **T.R. Vangberg:** None. **M.M. Gorecka:** None. **O. Vasylenko:** None. **K. Waterloo:** None. **C. Rodríguez-Aranda:** None.

Poster

064. Posture and Gait: Healthy Development and Aging

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Program#/Poster#: 064.02/FF17

Topic: E.06. Posture and Gait

Title: Frequency-dependent lower-limb coordination during standing is altered with age

Authors: *K. G. GRUBEN[1], A. DUTT-MAZUMDER[2]
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Abstract: Episodes of postural imbalance and falls increase with age and incur substantial social, economic, and medical costs. A key impediment to fall prevention is the currently insufficient understanding of the coordination mechanisms that enable humans to remain upright while standing. Traditional measures such as the center of pressure (CP) of the ground on foot force (F) excursion is inadequate to explain angular momentum control, and imprecision in joint torque and muscle activity estimations are unable to capture the subtle adjustments that maintain posture. We propose a novel approach that relates directly to sagittal-plane translational and rotational body motion by quantifying the relationship between the ratio of horizontal F to vertical F and CP. Remarkably, within 0.25 Hz frequency bands, that relationship is nearly linear indicating that the F vectors are directed at a point in space. The height of that intersection point (IP) varies with frequency, being located above the center of mass (CM) for <~2Hz and below the CM at higher frequencies. In a study of 27 young (<40 years) and 22 old (>60 years) human volunteers, the height of the IP was shown to be elevated (0.25 to 7 Hz). An elevated IP provides a greater moment about the CM that induces more angular acceleration toward the desired upright posture. This could be a compensation for deficits in other components of the postural control system (e.g. sensory degradation, processing delays, modified muscle properties). This novel quantification of the force which enables bipedalism may aid in detecting control modifications that relate to fall risk and thus suggest targets for therapeutic intervention.

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Poster

064. Posture and Gait: Healthy Development and Aging

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Topic: E.06. Posture and Gait

Support: Emerging Scholars Grant, School of Medicine and Health Sciences, George Washington University

Title: Novel divided-attention stepping intervention improves gait and modulates motion perception during fMRI in balance-impaired older adults

Authors: *S. J. LEACH[1], A. J. COLLEGIO[2], E. COSTELLO[1], S. SHOMSTEIN[2]
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Abstract: Fall prevention is an important public health goal. Many activities of daily living, including gait, require dual-tasks, which may result in a loss of balance, leading to falls. Impaired voluntary stepping also contributes to falls. The divided-attention timed stepping accuracy task (DATSAT) incorporates a multi-directional stepping task embedded with an information-processing component reflecting the demands of many functional tasks. The purpose of this study was to determine if DATSAT training results in changes in gait and perception of biological motion.

A pretest, posttest control group design was employed. Twelve older adults (66-85 years, 7 female) with increased fall risk were recruited for the study. Subjects were divided evenly via randomized block design to a control group, receiving no intervention; and experimental group, receiving DATSAT training 3 x per week for 12 weeks. The training was comprised of stepping 6 times to 16 randomly-sequenced targets as fast and accurately as possible. Stepping targets were at 60-80% of subject's maximal step length (MSL). Clinical outcomes included MSL, the six minute walk test (6MWT), gait velocity, stride length, and cadence. fMRI outcomes included changes in BOLD response from pre- to posttest in the middle temporal gyrus (MT) and superior temporal sulcus (STS). Participants passively viewed videos under 5 conditions in a block design: coarse/fine biological motion, coarse/fine non-biological motion, and still images taken from each motion condition.

Significiant clinical findings included a between group difference in the 6MWT (p=.003) and stride length (p=0.005). There was no between group difference in gait velocity (p=0.10), cadence (p=0.32) or MSL. Only the experimental group demonstrated within group differences in the 6MWT (p=0.043), MSL backwards (p=0.009) and MSL left (p=0.055). The experimental group showed a significant decrease (via fMRI) in activation from pretest to posttest in both left (p=0.007) and right (p=0.016) MT areas and right STS (p = 0.019). Importantly, experimental group showed a greater decrease than control group in activation from pretest to posttest in left MT ($p < 0.05$), right MT ($p < 0.01$), and right STS ($p < 0.05$).

The DATSAT intervention resulted in improvements in several gait parameters. In terms of changes in neural response, 12 weeks of DATSAT training elicited changes in motion perception areas of the cortex. Together, these findings suggest that improvement in motor output is achieved by a combined effect of increased gait control and biological motion perception.

Disclosures: S.J. Leach: None. **A.J. Collegio:** None. **E. Costello:** None. **S. Shomstein:** None.

Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.04/FF19

Topic: E.06. Posture and Gait

Support: NIH/NIAAA YIAA3009

Title: Correspondence of physical activity between wrist and ankle accelerometers: Associations with age and BMI

Authors: *V. RAMIREZ[1], E. SHOKRI-KOJORI[1], E. A. CABRERA[1], C. E. WIERS[1], D. TOMASI[1], G.-J. WANG[1], N. D. VOLKOW[2]
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Abstract: Physical Activity (PA) is associated with various aspects of physical and mental health and varies as a function of age and BMI. We aimed to compare PA measures obtained with wrist and ankle accelerometers and characterize their associations with age and BMI. Specifically, we assessed PA mean and PA variability (indexed by coefficient of variation (CV)) between and within subjects for seven consecutive days in 50 healthy participants. There were no differences in mean PA between wrist and ankle in daytime (p = .93) or nighttime periods (p = .26). However, CV of ankle PA during daytime was significantly higher than CV of wrist PA (p < .0001), while the opposite pattern was observed at nighttime (p < .0001). Mean daytime (but not nighttime) activity for wrist and ankle decreased significantly with age (p < .05). PA variability also decreased with age for wrist and ankle during daytime and for ankle during nighttime (p < .05). BMI was negatively associated with wrist daytime PA variability (p< .05). There were no significant gender effects for any of the activity measures. These findings indicate that wrist and ankle provide comparable measures of mean PA but show differences in PA variability. Age-related decreases in PA mean and variability were observed during daytime in both wrist and ankle, whereas higher wrist daytime variability was inversely associated with BMI. These findings provide new insight into specific PA features of both extremities that are associated with age and BMI. *Keywords:* Actigraphy, physical activity, mean, variability, accelerometer, aging, BMI.

Disclosures: V. Ramirez: None. **E. Shokri-Kojori:** None. **E.A. Cabrera:** None. **C.E. Wiers:** None. **D. Tomasi:** None. **G. Wang:** None. **N.D. Volkow:** None.

Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.05/FF20

Topic: E.06. Posture and Gait

Support: Saudi Arabia Ministry of Higher Education

Title: Effect of visual dependence and task loads on the Timed Up and Go test

Authors: *R. ALMAJID[1], E. A. KESHNER[2], E. V. VASUDEVAN[3], W. WRIGHT[1], C. TUCKER[1]
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Abstract: We aim to examine the kinematic properties of young and old adults performing a Timed Up and Go (TUG) test during additional attention demanding conditions. We will concentrate on the functional tasks that are part of the TUG test: sit to stand (SiTSt), turn, walk, and stand to sit (StTSi). A motor and visual tasks were added to the TUG test. A motor task of holding a half full glass of water and a visual task of viewing a scene of snowflakes moving in the pitch up or pitch down directions overlaid on the view of the room was added to the TUG test. Eight conditions were presented to 7 young (25.7±3.3 yrs) and 2 older healthy adults (69.5±6.2 yrs). These included: TUG, TUG with motor task (TUG_{motor}), TUG while wearing the Oculus Rift without additional tasks (TUG_{Oculus_Rift}), TUG while wearing the Oculus Rift with motor task ($TUG_{motor\_Oculus\_Rift}$), TUG with visual task in pitch up ($TUG_{visual(PitchUp)}$) and pitch down ($TUG_{visual(PitchDown)}$) directions, TUG with motor and visual tasks ($TUG_{motor\_visual(PitchUp)}$) and ($TUG_{motor\_visual(PitchDown)}$). Time to complete the task was recorded as were acceleration range SiTSt and StTSi, turning angular velocity and cadence, gait speed, arm swing and trunk peak velocities were recorded with Trigno™ wireless IMU sensors (Delsys Inc.). All adults walked slower ($p=0.001$) and longer ($p>0.001$) to complete the multitasking TUG tests compared to the standard TUG. In SiTSt and StTSi, they exhibited higher trunk pitch peak velocity in TUG compared to the other conditions ($P>0.001$) ($P>0.001$) and higher trunk yaw pitch velocity in SiTSt ($p=0.02$). In turning, subjects exhibited lower turning angular velocity in multitasking conditions ($p>0.001$), except TUG_{motor}, and lower cadence ($p=0.03$). Preliminary data show that SiTSt, StTSi, and turning elements of the TUG when combined with visual and motor tasks provide more information than the standard TUG test score, which is only time-based. Results will help clinicians to determine which activity is best to use in discriminating those who are at low and high risk of fall.

Disclosures: R. Almajid: None. **E.A. Keshner:** None. **E.V. Vasudevan:** None. **W. Wright:** None. **C. Tucker:** None.

Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.06/FF21

Topic: E.06. Posture and Gait

Support: NIH R21AG049615

Title: Motor prediction modulates protective balance and startle responses to sudden drop perturbations in older adults

Authors: *O. P. SANDERS, III, H. HSIAO, H. SINGH, D. N. SAVIN JR, R. A. CREATH, M. W. ROGERS
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Abstract: A sudden loss of ground support evokes rapid exaggerated neuromuscular reactions resembling startle-like reactions during first-trial responses (FTRs) that habituate with repeated exposure. FTRs induce large electromyographic (EMG) responses with increased muscle co-activation and lower extremity (LE) joint stiffness that affect fall landing. Excessive and less adaptable startle responses in aging can further disrupt protective balance responses to external perturbations. While startle-like effects in younger adults are modifiable during self-activated (SLF) drop perturbations due to motor prediction, the extent to which this capacity is retained with aging is unknown. To investigate this, seven older adults (72.46 ± 5.9 years) stood on a platform secured to a fixed frame by electromagnets, released via computer for externally triggered (EXT) trials or by a manual switch during SLF trials. Participants dropped 20cm onto a force platform. Bilateral muscle activity was recorded from the sternocleidomastoid, middle deltoid, biceps brachii, vastus lateralis, biceps femoris, gastrocnemius, and tibalis anterior. Blocks of 12 EXT trials were followed by 12 SLF trials 20 minutes apart to minimize habituation carryover. After the last SLF trial, participants received two EXT trials 20 minutes apart to assess retention (RTN) of modulation effects. Influence of motor prediction on landing strategy quantified by mechanical work. Mean EMG onset latencies for all conditions for upper extremity (UE) muscles occurred within 100ms of perturbation onset. No differences in mean muscle onset latencies between conditions or time points were observed ($p>0.05$). However, UE onset latencies during EXT FTR were earlier compared to SLF FTR. A common pattern was observed across conditions for UE muscles: mean EMG EXT FTR versus SLF FTRs were larger ($p<0.05$) and when compared to SLF FTR, mean EXT last trial responses (LTR) were smaller ($p<0.05$), indicating that EXT and SLF FTR comparisons were not likely due to habituation carryover effects. Furthermore, mean EMG FTR amplitudes for EXT versus RTN conditions were reduced ($p<0.05$). LE muscle response amplitudes were not different ($p>0.05$) between FTR and LTR between conditions. Mechanical work was reduced by (-20±3.1%) and (-12±4.7%) between EXT

FTR and SLF FTR and EXT LTR and SLF FTR respectively, indicating modulated landing strategy by motor prediction. These findings suggest older adults can modulate perturbation triggered startle/postural responses via motor prediction after experiencing SLF perturbations, and acutely retain these effects on subsequent RTN trials.

Disclosures: O.P. Sanders: None. **H. Hsiao:** None. **H. Singh:** None. **D.N. Savin Jr:** None. **R.A. Creath:** None. **M.W. Rogers:** None.

Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.07/FF22

Topic: E.06. Posture and Gait

Title: Can you walk and chew gum? The effect of chewing gum on gait dynamics in young and older adults

Authors: *B. S. SAMULSKI, S. MORRISON, J. PREBOR
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Abstract: Although walking is widely considered to be relatively autonomous task, it does require a degree of conscious involvement for optimal performance. As a result, an individual's gait can be negatively affected when performing another task concurrently (multi-tasking) as the CNS needs to allocate appropriate neural resources to both tasks for successful completion. Gait can be costly on neural resources and may limit successful participation in dual-tasking. While previous research has examined the impact of performing a cognitive task in combination with walking, there has been no specific research addressing the effect chewing could have on properties of gait. The aim of the study was to examine the impact of chewing at different rates on walking dynamics. Fifteen young adults and fifteen healthy older persons (over 60 years of age) participated in this study. Individuals were asked to chew gum while walking at their preferred speed. Four different conditions were performed; 1) walking while not chewing (control condition), 2) walking while chewing at the persons preferred rate, 3) walking while chewing at a faster rate (approximately 120Hz), and 4) walking while chewing at a slow rate (approximately 60Hz). Accelerometers were attached to the foot (to collect data related to heel strike) and on the side of the jaw (to collect data related to chewing motion). Surface muscle activity was also collected from the temporalis and masseter muscles during the chewing action. A 20 ft Protokinetics pressure sensitive walking surface was also used to collect gait metrics (i.e., gait speed, gait cadence, stride/step length, stride/step time). Overall, the results revealed a similar pattern for both the young and older subjects with each person's gait speed increasing to match the specified chewing rate. Consequently, the walking speed of all persons was greater for all chewing conditions compared to the control (i.e., no chewing) condition and similarly

reflected by significant changes in cadence and stride/step time. Further, cross correlation analysis revealed strong temporal coupling between chewing rates (jaw occlusion) and heel strike across all chewing conditions. Together these results indicate that the act of chewing has a strong driving influence on walking dynamics and that this coupling relation is unaffected by the normal process of aging. One possibility is that this tight coupling occurs in a top-down manner, with descending neural drive related to the jaw occlusion action during chewing entraining gait processes.

Disclosures: B.S. Samulski: None. **S. Morrison:** None. **J. Prebor:** None.

Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.08/GG1

Topic: E.06. Posture and Gait

Support: Internal program support

Title: The effects of internal versus external rhythmic cueing on gait performance in healthy adults

Authors: *E. C. HARRISON[1], M. E. MCNEELY[2], A. P. HORIN[3], G. M. EARHART[4]
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Abstract: Purpose: Movement and song have been paired together for centuries, and recent research reveals that regions of the brain that control movement overlap with those responsible for rhythm processing. Externally-generated cueing techniques (such as listening to music) accelerate and stabilize gait, but it is unknown if internally-generated cues (such as singing) produce the same motor benefit. This study explores the possibility that singing—either aloud or mentally—can ameliorate gait in the same way as listening to external cues, and offers insight into how internally-generated cues may enhance motor performance.
Method: 60 participants (30 male) were recruited into a healthy young (n=30, age: 25.8±2.8 years) and healthy old group (n=30, age: 64.9±7.2) years). Participants completed 3 trials in each of 5 gait conditions (uncued, listening to music, singing to music, singing aloud without music, and mental singing without music) done in forward and backward directions. The order of trials was randomized. The song used for cueing was 'Row, row, row your boat', and song tempo was adjusted to each participant's preferred walking speed.
Analysis: Gait characteristics (velocity, cadence, stride length) and variability (standard

deviations of stride length, step time, single support time) were compared in separate analyses for each walking direction. A 2-factor (group, gait condition) mixed model ANOVA was used to assess differences, and post-hoc pairwise comparisons were used as appropriate. Statistical significance was set at $p<0.05$.
Results: In healthy young adults, singing increased velocity and cadence in the backwards direction and decreased variability in both directions. For healthy older adults, singing increased cadence and stride length in the backwards direction. Both singing aloud and mental singing decreased variability measures in both forward and backward walking compared to musically-cued conditions.
Conclusion: These results suggest that matching movement to one's own voice via internally-generated cueing improves gait characteristics and reduces gait variability. Our novel approach using self-generated rhythmic cues to facilitate movement may provide important insight into treatment techniques for people with neurological disorders who have difficulty walking due to motor impairment. Motor improvement via sensorimotor synchronization to vocalizations may also further our understanding of auditory-motor coupling mechanisms within the brain.

Disclosures: E.C. Harrison: None. **M.E. McNeely:** None. **A.P. Horin:** None. **G.M. Earhart:** None.

Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.09/GG2

Topic: E.06. Posture and Gait

Support: P30AG028747

R01AG033607

Title: Transcranial direct current stimulation (tDCS) modulates hip abductor maximal isometric performance

Authors: *M. INACIO, R. CREATH, G. WITTENBERG, M. W. ROGERS
Physical Therapy and Rehabil. Sci., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Background. Aging brings about systemic changes that affect neuromuscular activation and motor performance. However, these changes may not affect all muscles of the lower limbs similarly. The hip abductor-adductor (AB-AD) musculature appears particularly vulnerable to composition changes and performance deficits that affect functional mobility and balance control. Transcranial direct current stimulation (tDCS) is commonly used to modulate cortico-spinal excitability and potentially neuromuscular activation. Given aging limitations in

activating muscles and the potential to enhance motor output using non-invasive brain stimulation, this study investigated the acute effects of tDCS on hip AB-AD neuromuscular and force-time performance during hip AB-AD isometric maximal voluntary contractions (IMVCs) in older adults.
Methods. 14 generally healthy community dwelling older adults (72.6±1.2yrs) underwent two tDCS sessions separated by at least 24h and an additional *no stimulation* session. In the three sessions, participants performed hip AB-AD and ankle dorsi-flexion (DF) isometric maximal voluntary contractions (IMVC) at 30º of hip AB and 90º of ankle dorsiflexion, on an isokinetic dynamometer. In the brain stimulation sessions, prior to the IMVC protocol, all participants received 2mA of anodal or cathodal tDCS for 20min over the leg representation on the primary motor cortex (M1) bilaterally. Surface electromyography (EMG) of the tibialis anterior (TA) was used as a surrogate for assessment of lower limb cortico-spinal excitability. A mixed effects model was used for between-session comparisons. Post-hoc pair-wise comparisons were performed with a LSD test and a Bonferroni correction. Significance was set at $p<0.05$.
Results. Cortico-spinal excitability showed only a positive trend after anodal tDCS ($p>0.05$), but was significantly decreased by cathodal tDCS (17%, $p<0.05$). Hip AB peak torque was significantly reduced after cathodal tDCS compared to anodal tDCS and *no stimulation* (12% and 8% respectively, $p<0.05$) and marginally improved after anodal when compared with *no stimulation* (4%, $p=0.076$). Anodal tDCS significantly increased hip AB rate of torque development over cathodal and *no stimulation* sessions (55% and 28% respectively, $p<0.05$).
Conclusions. tDCS modulated maximal hip abductor peak torque and moreover increased hip abductor rate of torque development. These enhancements of motor performance may have useful implications for rehabilitation approaches to improve balance control and functional mobility.
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Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.10/GG3

Topic: E.06. Posture and Gait

Support: California Physical Therapy Fund

Title: Is functional organization of the motor cortex associated with timing of anticipatory postural adjustments in healthy young and older adults?

Authors: *J. ARMOUR SMITH[1,3], A. ALBISHI[3], N. AHMED[2], B. E. FISHER[3]
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Abstract: Introduction: Anticipatory postural adjustments (APAs) in the axial musculature are a key component of postural control. The onset of APAs in the trunk and hip muscles may be delayed in older adults, but the mechanisms underlying this delay are unclear. Altered spatial representation of axial muscles in the motor cortex may underlie delayed postural muscle recruitment with aging. The purpose of this study was to examine the relationship between trunk and hip muscle representation in primary motor cortex and postural motor behavior in healthy young and older adults. We hypothesized that the overlap of the motor representations of trunk and hip musculature would be greater in older than young adults and that the extent of overlap would be significantly correlated with the timing of anticipatory muscle activation during rapid arm raising. Methods: Eleven young adults (mean (SD) age 25.5 (±2.1 years) and eight older adults (mean (SD) age 71.5 (±7.8) years) performed rapid arm abduction with their non-dominant arm. Activity in the contralateral external oblique (EO), lumbar paraspinals (LP), gluteus medius (GMED) and ipsilateral deltoid (DELT) was recorded using surface electromyography. Latency of anticipatory muscle activity relative to DELT onset was calculated in a window 100ms before to 50ms after DELT onset. The center of gravity for the cortical representation of all three muscles was mapped from the amplitude of motor evoked potentials obtained during sub-maximal contractions using single-pulse transcranial magnetic stimulation. Overlap of the muscle representations was then calculated as the distance between the centers of gravity for the three muscles (separation distance). Results: Anticipatory activity in the GMED was significantly later in the older than the young adults ($p=0.03$) but was not significantly altered in LP or EO ($p=0.54$ and $p=0.49$ respectively). There was no significant difference in average separation distance between the age groups ($p=0.99$). In the young adults, there was a significant correlation between average separation distance and average latency ($r=-0.6$, $p<0.05$), with greater distance between muscle representations associated with earlier onset of muscle activity. This relationship between latency and separation distance was not present in the older adult group ($r=0.1$, $p=0.86$). Conclusions: Healthy older adults do not demonstrate greater overlap of cortical representation of axial muscles than young adults. However, cortical influence on the timing of coordinated muscle activity during APAs may be greater in young adults.

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Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.11/GG4

Topic: E.06. Posture and Gait

Title: The characteristic of gait in children during dual-task conditions

Authors: *C. W. CHAU, L. BRICK, J. CRUMLISH, C. DELANEY, D. SANCILIO
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Abstract: It has previously been shown that walking requires executive and attentional functions and that gait decrements result when the attentional demands of the concurrent tasks exceed the attentional resources available (Woollacott and Shumway-cook, 2002). Children and individuals with balance deficits were more vulnerable to interference from a concurrent task during locomotion than healthy adults. This study investigates the gait characteristics of typically developing 5 and 6 year old (yo) children while performing a concurrent cognitive task. Thirty-one kindergartners enrolled in New York State public school (16 male and 15 females) performed two cognitive tasks, a verbal counting backwards (VCB) task where they count backwards from 10 to 1, and a verbal sound recognition (VSR) task where they identify different familiar sounds played. Then, subjects walked on the GAITRite (CIR System Inc. NJ), a portable carpeted walkway (2X14ft) embedded with electronic pressure sensors that record footprints and allowing us to measure spatiotemporal gait parameters. Each subject completed 3 trials of walking without a concurrent task (Single-Task (ST)) or with a concurrent cognitive task (Dual-Task (DT)), either DT-VCB or DT-VSR in a randomized order. The only constraint for all walking tasks is that the child may not stop on the gaitrite. Data from 5 and 6yo were pooled and ANOVA was used to compare the spatiotemporal parameters of the three walking conditions. Results showed a significant decrease in velocity during DT-walking for both VCB (-23.5 cm/s) and VSR (-44.2 cm/s) task as compared to ST-walking. A significant decrease in cadence (-24 steps/min), step length (-12 cm), stride length (-23.5cm), swing (-3.4%) and single support duration (-2.7%), and a significant increase in step cycle (+187ms), stance (+3.4%) and double support (+6.6%) duration was found during DT-VSR walking as compared to ST-walking. Stride-to-stride variability in velocity and stride length is decreased in 6yo as compared to 5yo. Our results suggest a decrease in gait stability in children during DT-VSR walking and that VSR exerted a greater interference on locomotion in children than VCB task. The VSR task involves processing of an auditory stimuli as well as executive function exerting a higher cognitive load than the VCB task which may result in greater gait decrements. Increase in step variability suggests a reduced regularity, stability and efficiency. A decrease in gait variability in 6yo as compared to 5yo children suggests that developmental maturation may play a role in the ability to adapt the locomotor pattern to a concurrent cognitive task.

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Poster

064. Posture and Gait: Healthy Development and Aging

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 064.12/GG5

Topic: E.06. Posture and Gait

Title: Characterization of sensory function associated with idiopathic toe walking in children

Authors: *V. W. CHU
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Abstract: Toe-walking is characterized by the absence of heel contact during gait. Children who consistently toe-walk after 3 years old are considered idiopathic toe-walkers, when there is no medical cause for the toe-walking. Long term consequences of persistent toe-walking include shortened Achilles tendon and ankle equinus, which can lead to abnormal gait patterns, posture, and balance problems in adulthood. Clinicians and researchers have suggested a link between idiopathic toe-walking and sensory processing dysfunction, but, to date, there is limited research examining this relationship. Areas of sensory processing that potentially relate to toe-walking include: sensory seeking behaviors, tactile defensiveness, poor proprioceptive awareness, vestibular dysfunction and difficulties with sensory modulation.
Identifying the specific sensory function that underpin toe walking in children will be a valuable contribution to the development of specific diagnoses and treatments for this gait abnormality. We developed a set of assessments that can be used to differentiate subtypes of sensory dysfunction profiles related to toe-walking. Balance-related proprioceptive, vestibular and visual processing is assessed through the Sensory Organization Test. Tactile processing is measured with vibration perception threshold using an electrical tuning fork that increases in vibration magnitude and tactile threshold using the Semmes Weinstein filaments. Proprioceptive processing is assessed by testing joint position sense and movement sense in matching leg movements without looking at their legs, and force perception by pressing on foot pedals to match target forces without feedback. Sensory modulation response to stimuli is examined by measuring skin conductance in response to textures presented to the feet (tactile), tilt in place while seated (vestibular). The sensory measurements are then examined with respect to measured gait kinematics, frequency and amount of toe-walking in the community.
This set of comprehensive tests allows us to characterize sensory processing patterns that relate to idiopathic toe-walking. Currently, there is no comprehensive evidence-based framework for the underlying causes of idiopathic toe-walking. This research will significantly advance the research and clinical fields by providing a standardized framework to detect and analyze the underlying sensory deficits in these children. Our research strives to better understand the causes of idiopathic toe-walking, so that we can develop more effective treatment strategies to guide earlier intervention to prevent long term consequences of persistent toe-walking.

Disclosures: V.W. Chu: None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.01/GG6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CIHR15129 and 15176

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FRQS 5249

DAAD Scholarship to SG

Title: A neural substrate involved in stopping locomotion

Authors: *S. GRÄTSCH[1,2,3], O. DEMERS[2], F. AUCLAIR[1], D. VEILLEUX[1], A. BÜSCHGES[3], R. DUBUC[1,2]
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Abstract: Locomotor movements are controlled by specific centers in the brain. In vertebrates, the mesencephalic locomotor region (MLR) is one such center. It controls locomotor activity via excitatory projections onto reticulospinal (RS) neurons that in turn activate spinal central pattern generators (CPGs) for locomotion. Supraspinal mechanisms that initiate and maintain locomotion have been studied for decades, whereas those controlling termination of locomotion have only been examined recently. In mice and lampreys RS cells (Stop Cells) were found to halt locomotion when activated [Bouvier et al., 2015, Cell 163(5):1191-1203; Juvin et al., 2016, Cell Rep. 15(11):2377-2386]. Intracellular recordings of Stop Cells in the lamprey revealed a characteristic activity pattern, comprising a termination burst that is linked with the end of swimming. Here we aimed at identifying neural inputs that could be linked to this characteristic termination burst observed in Stop Cells. Because the MLR provides significant inputs to RS cells, it is a logical candidate. We performed experiments in lamprey semi-intact preparations (n=50) in which intracellular recordings of RS cell activity were performed and then correlated to the active body movements. We found that the bursting pattern of Stop Cells was clearly correlated to the intensity of the MLR activation. The number of spikes increased linearly with MLR stimulation intensity. We also found that swimming could be stopped by stimulating the

MLR electrically and pharmacologically. Electrical stimulation of the MLR initiated swimming that often exceeded the stimulation period (19.37±1.24s). A second MLR stimulation at a lower intensity (50% of control) and delivered later during the swimming bout, halted locomotion (within 6.7±0.37s). Stop Cells displayed a termination burst in response to the low intensity MLR stimulation. On the other hand, MLR stimulation at the same intensity as the initial stimulation (100% of control) prolonged the ongoing locomotor bout. Similar effects were seen for sensory-evoked and spontaneous locomotion. Injections of small quantities of D-glutamate in the MLR during the swimming bout had the same effects than electrical stimulation: it halted the ongoing locomotor bout. Anatomical experiments identified a population of candidate MLR cells that could underlie the function described above. Detailed connectivity was further examined electrophysiologically. Taken together, our results indicate that the MLR not only is able to control initiation and maintenance, but also termination of swimming.Funding: Funded by CIHR, NSERC and GLFC. SG received studentships from DAAD, UzK.

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Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.02/GG7

Topic: E.07. Rhythmic Motor Pattern Generation

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FRQS 5249

Title: Dopaminergic modulation of odor-evoked motor commands in lampreys

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Abstract: Detection of chemical cues is important to navigate in the environment and guide locomotion towards appetitive targets and away from danger. A neural pathway generating odor-evoked swimming was characterised in the lamprey (*Petromyzon marinus*), a basal vertebrate

(Derjean *et al.* 2010; PLoS Biol 8(12): e1000567). It comprises projections from the medial part of the olfactory bulb (OB) to the posterior tuberculum (PT). The signal is then relayed to the mesencephalic locomotor region and eventually reaches reticulospinal (RS) cells, which activate the spinal locomotor networks. We recently found that this pathway is under a tonic GABAergic inhibition in the medial OB (Daghfous *et al.* 2013; Chem Senses 38(7): e1-e124). Additional modulatory mechanisms might exist in the OB of lampreys as it also contains dopaminergic (DA) fibers, whose impact on olfactory transmission is unknown. This study was aimed at (1) mapping precisely the DA innervation of the OB and (2) characterizing its effects on the olfactory-motor pathway. (1) DA immunofluorescence showed scarce innervation of the OB, mostly seen in its medial part. In larval and adult specimens, DA fibers neighboured the medial glomeruli and were observed in close vicinity to olfactory nerve fibers and OB projection neurons. No DA-immunoreactive cell bodies were detected in the OB in our material. Dopaminergic neurons labelled by tracer injections in the medial OB were located in the PT, suggesting bidirectional communication between these two regions. Double-labelled neurons were also observed in the periventricular hypothalamus. (2) Synaptic responses of RS cells to electrical stimulation of the olfactory nerve were recorded intracellularly in isolated whole-brain preparations. Local injection of DA in the medial OB induced a decrease of RS cell responses, suggesting that DA modulation of the medial OB inhibits odor-evoked locomotion. Furthermore, either D1-like (dihydrexidine) or D2-like (quinpirole) receptor agonist injections yielded similar results, indicating that both families of DA receptors are involved. On the other hand, injections of either the D1-like (SCH 23390) or the D2-like (eticlopride) receptor antagonist produced inconsistent results, suggesting that there is no tonic inhibitory DA modulation. When the RS cell responses were increased following a prior injection of a $GABA_A$ receptor antagonist (GABAzine), the effects of DA agonists were considerably increased even supressing large bursts of action potentials. Altogether, these results show the presence of a DA innervation within the medial OB of the lamprey, which modulates olfactory inputs to the motor command system.

Disclosures: **P. Beausejour:** None. **C. Ngovandan:** None. **F. Auclair:** None. **D. Veilleux:** None. **G. Daghfous:** None. **B. Zielinski:** None. **R. Dubuc:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

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Program#/Poster#: 065.03/GG8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Seed Grant 362804 from The University of Texas System Neuroscience and Neurotechnology Research Institute

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Russell and Diana Hawkins Family Foundation Discovery Fellowship

Title: Voltage-sensitive dye (VSD) recordings provide insights into the differential modification of spike frequency and burst timing that underlies L-DOPA mediated motor pattern selection in the feeding circuit of *Aplysia*

Authors: *R. M. COSTA, C. L. NEVEU, R. HOMMA, S. NAGAYAMA, D. A. BAXTER, J. H. BYRNE
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Abstract: A general model for behavioral selection considers neural circuits to be multifunctional and selection to be mediated via modulation of neuronal subgroups within the circuit. To gain insights into the ways in which motor patterns are selected, we monitored activity in the buccal ganglia of *Aplysia* using a voltage sensitive dye (VSD) while varying the concentration of L-DOPA to select from among different buccal motor patterns (BMPs). Up to 120 cells were monitored in each preparation. Activity was monitored for 2 min immediately after a 15 min treatment period with either 40 µM L-DOPA (low L-DOPA), 250 µM L-DOPA (high L-DOPA) or vehicle (control). Preference for intermediate patterns was significantly greater in low L-DOPA (66.47 ± 9.37%, mean ± standard error, n = 7 preparations, a total of 294 neurons) than control (0.00 ± 0.00%, n = 7, 328 neurons) or high L-DOPA (7.18 ± 4.16%, n = 7, 379 neurons). In contrast, the preference for bite-like patterns was significantly greater in high L-DOPA (81.35 ± 9.34%) compared to control (22.62 ± 9.40%) or low L-DOPA (20.01 ± 4.22%). The overall number of BMPs was also significantly increased in high L-DOPA (15.29 ± 2.40) compared to control (3.43 ± 0.37), but the increase in low L-DOPA (7.71 ± 1.23) was not significant. Motor pattern selection was accompanied by differential modulation of neurons active during the protraction or retraction phases of a BMP. The selection of intermediate BMPs was associated with a decrease in burst duration but no change in spike frequency in neurons active during retraction, while no change occurred in spike frequency or burst duration in neurons active during protraction. In contrast, the selection of bite-like BMPs was associated with an increase in spike frequency but no change in burst duration in neurons active during protraction, and conversely a decrease in burst duration but no change in spike frequency in neurons active during retraction. These results suggest that individual groups of neurons are modified in characteristic ways to mediate a switch in behavior.

Disclosures: **R.M. Costa:** None. **C.L. Neveu:** None. **R. Homma:** None. **S. Nagayama:** None. **D.A. Baxter:** None. **J.H. Byrne:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.04/GG9

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Interneuronal control of extrinsic modulation in the feeding system of Lymnaea

Authors: *D. PRICE, M. CROSSLEY, G. KEMENES, P. BENJAMIN, T. NOWOTNY, I. KEMENES
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Abstract: Feeding in the pond snail (*Lymnaea stagnalis*) is controlled by a complex and distributed network of neuron types. This includes modulatory neurons that act on multiple functional groups that either promote or prevent feeding. The most thoroughly studied of these is the cerebral giant cell (CGC), which plays a permissive role in feeding, increasing excitatory output to the system when the animal senses food. Another modulatory cell, the pleural-buccal interneuron (PlB), has the opposite effect, increasing inhibitory output when the animal receives an aversive touch. The cerebral ventral 1a (CV1a) cell type also modulates feeding and when active can drive a feeding rhythm.
A previously unidentified neuron, termed parietal dorsal 4 (PD4), has now been discovered, which can alter the activity of all three of these modulatory neurons, thus giving strong influence over the entire feeding system. Electrophysiological recordings of PD4 in the isolated brain show a relatively negative resting potential with no spontaneous action potentials. Extracellular stimulation of the lip nerves causes PD4 to become active both during the pulse and for several seconds afterwards, indicating a prolonged modulatory effect that exceeds the input.
Action potentials in PD4 result in short latency 1:1 EPSPs on both the ipsilateral and contralateral cerebral giant cells (CGC), suggesting a monosynaptic excitatory synapse. Longer latency excitation and inhibition of the ipsilateral CV1a and PlB respectively, can also be seen. Together these synaptic effects promote feeding and short excitatory pulses of PD4 are sufficient to cause feeding cycles.
These findings suggest that the functional role of PD4 is to integrate sensory inputs to determine whether the animal should feed. Importantly our experiments provide information about both the input and the output of this modulatory feeding interneuron.

Disclosures: D. Price: None. **M. Crossley:** None. **G. Kemenes:** None. **P. Benjamin:** None. **T. Nowotny:** None. **I. Kemenes:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS029436 (MPN)

NS 17813

Title: Modulation of the pyrokinin-elicited gastric mill rhythm by an endogenous peptide hormone and a proprioceptive neuron

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Abstract: Different sources of modulation can change the cellular/synaptic properties of network neurons differently yet enable that network to generate similar output patterns. Little information is available regarding how such differences in network component properties influence how networks respond to perturbations. We are addressing this issue using the gastric mill (chewing) circuit in the isolated stomatogastric ganglion (STG) of the crab *Cancer borealis*. Stimulating the projection neuron MCN1 or bath applying the endogenous neuropeptide CabPK (not present in MCN1) elicits a similar gastric mill rhythm (GMR) via different cellular/synaptic mechanisms (Saideman et al, 2007 J Neurosci; Rodriguez et al, 2013 J Neurosci). The influence of two perturbations, superfusing the peptide hormone CCAP and stimulating the proprioceptive GPR neuron, were studied on the MCN1-driven network state (Delong et al. 2009ab, J Neurosci, J Neurophysiol). CCAP slows the MCN1-GMR by selectively prolonging the protraction phase, while GPR slows the MCN1-GMR by selectively prolonging retraction. Here we determine how these two inputs influence the CabPK-elicited GMR.
1µM CCAP application decreased retraction duration of the CabPK-GMR without altering protraction duration ($p < 0.05$, $n = 15$), unlike its influence on the MCN1-GMR. The decrease in retraction duration resulted in a significant decrease in the cycle period of the rhythm ($p<0.05$, $n = 15$). In contrast, the CabPK-GMR response to GPR stimulation was comparable to the MCN1-GMR response. Specifically, GPR selectively prolonged the retraction duration during the CabPK-GMR ($p < 0.05$, $n = 4$), which slowed the rhythm in all four experiments ($p = 0.07$, $n = 4$). Interestingly, despite the same GPR response occurring during both GMRs, the underlying synaptic mechanism is likely different because, during the MCN1-GMR, GPR inhibits the STG terminals of MCN1 and MCN1 is not active during the CabPK-GMR. These results suggest that the consequence of the same perturbation on similar activity patterns generated by different

network states is not predictable. We aim to extend these results and determine the cellular/synaptic mechanisms underlying the CabPK-GMR response to these perturbations.

Disclosures: D.J. Powell: None. **E. Marder:** None. **M.P. Nusbaum:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS029436 (MPN)

Title: The same microcircuit responds differently to the same circulating hormones when generating two different motor patterns

Authors: *M. P. NUSBAUM, A. P. COOK
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Abstract: The impact of parallel modulatory actions on microcircuit output is poorly understood. To better elucidate this issue, in a behavioral context, we take advantage of the partially open circulatory system of the crab, *Cancer borealis*, to extract its hemolymph (blood) and apply it directly to the stomatogastric ganglion (STG) isolated from a different *C. borealis*. Crab hemolymph contains many hormones, some of whose amounts are changed by feeding state (Schmerberg et al, 2015 ACS Chem Neurosci). Using this approach, hemolymph extracted from a recently fed crab, but not from an unfed crab, reversibly slows the VCN (ventral cardiac neuron)-triggered gastric mill (chewing) rhythm (GMR) by prolonging both phases (protraction, retraction) of the motor pattern, without weakening circuit neuron activity (Temporal et al, 2015 SFN Abstract). Not all circuit neuron activity was prolonged, however, indicating the chewing motor pattern also changed.
The POC (post-oesophageal commissure)-triggered GMR responds differently to unfed hemolymph application, despite both GMRs being driven by the same two projection neurons (MCN1, CPN2) and generated by the same circuit neurons (Blitz & Nusbaum, 2008 J Neurosci; White et al, 2011 J Neurosci). While unfed hemolymph does not alter the VCN-GMR (Temporal et al, 2015), it either reversibly suppressed the POC-GMR (cycle period: pre-hemolymph, 17.7 ± 1.5 s; hemo, 0 ± 0 s; post-hemo, 15.9 ± 2.5 s; n=5) or consistently reduced its duration (# cycles: pre-hemo, 97.6 ± 20.9; hemo, 23.0 ± 2.2; n=5/5, p=0.02). During both outcomes, MCN1 was equally activated in saline and hemolymph, as for example when no POC-GMR was elicited (pre-hemo: 11.7 ± 1.0 Hz; during hemo: 11.1 ± 0.9 Hz; post-hemo: 12.0 ± 1.0 Hz; n=5, p=0.21). During the same hemolymph applications when no POC-GMR was elicited, the VCN-GMR was subsequently elicited (n=3/3). At these times, MCN1 exhibited a faster firing rate than following

POC stimulation (post-VCN: 19.2 ± 0.4 s, n=3). These results suggest that the unfed hemolymph action on the POC-GMR occurs downstream of MCN1/CPN2 activation (e.g. it influenced their STG terminals and/or altered STG neuron properties in a manner which only affected the POC-GMR), and its differential sensitivity may be a consequence of the lower MCN1 firing rate relative to the VCN-GMR. We aim to first pursue these possibilities by (a) artificially driving a POC-GMR with a VCN-equivalent MCN1 firing rate, and (b) determining the unfed hemolymph influence on the cellular/synaptic properties of the gastric mill rhythm generator neurons (LG, Int1; White et al, 2011). Future studies will include identifying the hormones responsible for these actions.

Disclosures: M.P. Nusbaum: None. **A.P. Cook:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.07/GG12

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Miami University Biology Department

Title: State-dependent sensory actions on network inputs

Authors: *D. M. BLITZ
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Abstract: Sensory feedback enables motor systems to adapt rapidly to changes in the environment of an organism. In rhythmic motor systems, sensory feedback alters motor activity through actions on motor networks and on projection neuron inputs to the networks. Activation of a motor system can alter the influence of sensory feedback. Although this can occur at the network or projection neuron level, there is less known about regulation of sensory feedback acting at the projection neuron level. In some instances, the same projection neurons are activated by different pathways to produce different network outputs. Yet, it is not known if gating of sensory feedback to projection neurons occurring during activation of one version of network output, occurs during all versions of network activity. To address this question, I use the stomatogastric nervous system (STNS) in the Jonah crab, *Cancer borealis*. The STNS is a well-described rhythmic motor system controlling chewing and filtering of food. In addition to identified network and projection neurons, there are identified sensory neurons that act at network and projection neuron levels. For instance, when the chewing network is silent, GPR sensory neurons excite the projection neurons MCN1 and CPN2, which activate the chewing network. In a long-lasting chewing pattern triggered by the VCN modulatory pathway, GPR actions on MCN1 and CPN2 are gated out (Beenhakker et al, J Neurosci, 2007). However, GPR

effects on chewing triggered by the POC modulatory pathway suggest that GPR actions on MCN1 and CPN2 are not gated out in this state (White and Nusbaum, SfN abstract, 2009). In fact, during POC-chewing GPR increased MCN1 (p=0.001, n=13) and CPN2 (p=0.001, n=9) activity rates and altered their activity patterns (p=0.012-0.029, n=9-13). To explore this state-dependence of GPR actions, I investigated the mechanism(s) by which GPR influences MCN1/CPN2 activity. As in other rhythmic motor systems, the chewing network provides feedback to its projection neuron inputs. In three preparations, GPR elicited a transient increase in feedback strength (49 to 58pA; 105 to 168pA; 7 to 104pA). Further, when GPR was not able to act through network feedback, it elicited a lower CPN2 firing rate (p=0.02, n=4). These results indicate that transient changes in network feedback strength contribute to rapid adaptive changes in motor output. Additionally, network feedback strength increases during VCN-chewing (Blitz, J Neurophysiol, 2017), but decreased during POC-chewing (p=0.02, n=2). Thus, future studies will explore whether the modulatory status of network feedback contributes to state-dependence of sensory feedback.

Disclosures: D.M. Blitz: None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

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Support: ERC Advanced Grant

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Title: Locomotor speed control circuits in the caudal brainstem

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Abstract: Locomotion is a universal behavior providing animals with the ability to move between places. Many brain regions encode locomotor parameters but how the nervous system translates plans to move into actions remains poorly understood. In previous work, we described the existence of a complex connectivity matrix between specific brainstem subregions and motor neurons in the spinal cord (Esposito, Capelli and Arber 2014, Nature 508, 351-356). We hypothesized that motor command lines in the brainstem may be organized into modules and functionally linked to the implementation of diverse motor programs. Here we identify functionally heterogeneous neuronal subpopulations in the caudal medulla dissociable by

neurotransmitter identity, connectivity and location. To determine the behavioral impact of identified neuronal subpopulations, we took advantage of optogenetic manipulators, applying combinatorial use of mouse genetics and viral targeting strategies. We found that optogenetic activation of a specific cluster of glutamatergic neurons in the ventral medulla positively regulates locomotor speed, whereas activation of inhibitory neurons produces behavioral arrest. Furthermore, loss-of-function experiments demonstrate the necessity of the identified glutamatergic subpopulation in the performance of high-speed locomotion. Anatomically, we found that identified excitatory and inhibitory subpopulations are regulated by differential upstream inputs and communicate with distinct circuits in the spinal cord. Notably, excitatory medullary neurons receive synaptic input originating from mesencephalic locomotor region (MLR) subcircuits, and elimination of excitatory medullary neurons attenuates the strength of the locomotor output signal from the MLR. Together, our work demonstrates the existence of precisely organized yet spatially intermingled neuronal circuit elements in the brainstem and their involvement in the regulation of locomotor speed.

Disclosures: **P. Capelli:** None. **C. Pivetta:** None. **M. Esposito:** None. **S. Arber:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

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Title: Spinal neurons mediating effect of epidural stimulation of the spinal cord on locomotor network

Authors: T. DELIAGINA[1], P. E. MUSIENKO[2,3], O. V. GORSKII[2,3], V. F. LYALKA[1], N. MERKULYEVA[2,3], Y. P. GERASIMENKO[2], *P. V. ZELENIN[1]
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Federation; [3]Inst. of Translational Biomedicine, St Petersburg State Univ., St. Petersburg, Russian Federation

Abstract: Electrical epidural stimulation (ES) of the spinal cord can evoke locomotion in animals with spinal cord injury as well as in decerebrate animals with intact spinal cord. It was suggested that ES excites sensory fibers within the dorsal roots resulting in activation of the locomotor network. *The aim of the present study* was to reveal spinal neurons mediating effect of ES on the locomotor network. For this purpose, in decerebrate cats activity of spinal interneurons from L4-L6 was recorded during locomotion caused by ES of the spinal cord at L5.
To reveal neurons contributing to activation of locomotor network, reaction of individual neurons to beginning of ES was analysed. For this purpose spontaneous activity of a neuron was compared with its activity in the initial period of ES (before generation of the first step). According to their reaction, two groups of neurons were revealed. Group A neurons exhibited 3-4 fold increase in their activity at the beginning of ES. By contrast, activity of Group B neurons did not change before generation of the first step. Group A neurons constituted 38% of all neurons with activity modulated in locomotor rhythm, and 45% of all non-modulated neurons. Both modulated and non-modulated Group A neurons were found in all studied spinal segments, in different parts of the gray matter and intermixed with Goup B neurons. We suggest that Group A neurons mediate activation of spinal locomotor networks caused by ES.
To reveal neurons contributing to maintenance of locomotor network excitability sufficient for generation of locomotion, post-epidural stimulus histogram was built for individual neurons. We found that 7% of neurons did not respond to epidural stimuli and 8% of neurons had an inhibitory response. We suggest that these neurons do not contribute to maintenance of the excitability of the locomotor network. In 14% of neurons excitatory and in 71% of neurons, both excitatory and inhibitory responses were observed. We suggest that neurons with excitatory response, as well as those with predominant excitatory response, can contribute to the maintenance of locomotor network excitability level during ES stimulation. We found that in 68% of neurons, which had both excitatory and inhibitory responses, the predominant response was excitatory. Both purely and predominant excitatory responses were significantly larger in Group A modulated neurons, as compared to those in Group B modulated neurons. Thus we suggest that Group A modulated neurons strongly contribute to initial activation, as well as to maintenance of the high level of excitability of locomotor network during ES.

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Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

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StratNeuro

Swedish Brain Foundation FO2016-0007

Title: Spinal cholinergic interneurons differentially control motoneuron excitability and alter the locomotor network operational range

Authors: *M. BERTUZZI, K. AMPATZIS
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Abstract: While cholinergic neuromodulation is important for locomotor circuit operation, the specific neuronal mechanisms that acetylcholine employs to regulate and fine-tune the speed of locomotion are largely unknown. Here, we show that cholinergic interneurons are present in the zebrafish spinal cord and differentially control the excitability of distinct classes of motoneurons (slow, intermediate and fast) in a muscarinic dependent manner. Moreover, we reveal that m2-type muscarinic acetylcholine receptors (mAChRs) are present in fast and intermediate motoneurons, but not in the slow motoneurons, and that their activation decreases neuronal firing. We also provide evidence that this configuration of motoneuron muscarinic receptors serves as the main intrinsic plasticity mechanism to alter the operational range of motoneuron modules. These unexpected findings provide new insights into the functional flexibility of motoneurons and how they execute locomotion at different speeds.

Disclosures: M. Bertuzzi: None. **K. Ampatzis:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: BBSRC (BB/M024946/1)

BBSRC (BB/JO1446X/1)

University of St Andrews

Title: Ih current in excitatory descending interneurons of the Xenopus tadpole spinal swim network

Authors: L. D. PICTON[1], *H. ZHANG[2], K. T. SILLAR[3]
[1]Univ. of St Andrews, St Andrews, United Kingdom; [2]Ctr. for Neuroregeneration, Univ. of Edinburgh, Edinburgh, United Kingdom; [3]Univ. St Andrews, St Andrews, United Kingdom

Abstract: Descending interneurons (dINs) provide the excitatory drive for rhythm generation in the spinal central pattern generator (CPG) controlling swimming in *Xenopus* frog tadpoles. dINs display distinct properties compared to other spinal interneurons, such as: a more depolarised resting membrane potential; a lower input resistance; highly reliable firing of a single action potential per swim cycle; post-inhibitory rebound; and pacemaker-like properties (Roberts, Li & Soffe, 2010, 2012).
Using whole-cell patch clamp recordings in current clamp mode from immobilised stage 42 *Xenopus* larvae, we show that dINs also display evidence of an Ih current (*hyperpolarisation-activated cation current*), as indicated by the presence of a hallmark depolarising voltage sag in response to membrane hyperpolarisation. Sag potentials in dINs were blocked by ZD7288 (50 μM), providing evidence that they are mediated by the voltage-dependent HCN channels known to underlie Ih activation. ZD7288 also hyperpolarised dINs by approximately 10 mV, accompanied by a significant increase in input resistance; indicating that Ih current is active at rest in members of the dIN population. Block of Ih using ZD7288 also revealed a slowly recovering membrane hyperpolarization in dINs following swimming, indicating a post-swim hyperpolarizing current was masked by Ih. Other spinal interneuron types were found to display evidence of Ih only at very hyperpolarized, and non-physiological membrane potentials. Although ZD7288 blocked the sag current in these neurons, the resting membrane potential was not affected.
Using ventral root recordings, bath application of ZD7288 (50 μM) or caesium significantly decreased evoked swim episode duration and disrupted the fast swimming rhythm, causing bursts to become slower, longer and more variable. Upon washout of ZD7288, a novel spontaneous swimming rhythm with a regular interval emerged.
Using simultaneous patch-clamp and ventral root recordings we found that disrupted swimming was accompanied by uncharacteristic spike failures in dINs, which coincided with periods of tonic spiking in non-dIN interneurons. Thus, Ih current appears to contribute to the fidelity of spiking in dINs, which has knock-on effects for spiking in interneurons throughout the swim network. One possibility is that Ih contributes to the phasic post-inhibitory rebound mechanism that generates spikes in dINs during swimming, which is fundamental to rhythm-generation in the *Xenopus* spinal cord.
References: Roberts et al. 2010. *Front Behav Neurosci, 4*, 16. Roberts et al. 2012. *Dev Neurobiol,72*, 575.

Disclosures: L.D. Picton: None. **H. Zhang:** None. **K.T. Sillar:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

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Program#/Poster#: 065.12/GG17

Topic: E.07. Rhythmic Motor Pattern Generation

Support: BBSRC (BB/M024946/1)

University of Edinburgh

Title: Altering swimming speed by the spinal motor circuit of Xenopus larvae

Authors: *F. JACQUOT[1], H. ZHANG[2]
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Abstract: The ability to change speed, direction and strength in locomotor behaviours, like walking and swimming, is vital for animals and humans in everyday life. In vertebrates, these rhythmic movements are controlled by central pattern generator (CPG) networks in the spinal cord, and such an ability is obtained during early development. Using a simple model, the spinal cord of *Xenopus* tadpoles, we aim to address how swimming speed and strength are altered by the spinal CPG network. Previous studies show that the spinal CPG of immobilized *Xenopus* embryos (2 days old) generates a stereotypical fictive swimming activity (motor output without muscle contraction), which starts at higher frequency (~25Hz) and gradually decreases until the end of swimming. A day later, the *Xenopus* larvae CPG can produce a much more flexible swimming pattern with periodic changes in motor burst frequency and amplitude (Issberner & Sillar 2007).
To test the role of spinal circuit in the control of swimming frequency, *Xenopus* larvae were lesioned in the hindbrain at the otic level and then their subsequent swimming pattern was examined. Just 13% of lesioned larvae (4 out of 30) were still able to exhibit the flexible larval swimming pattern, whereas 87% displayed the stereotypical embryonic motor pattern. This suggests that the spinal CPG network itself can alter motor speed, but descending inputs from higher brain centres play an important role in modulating motor patterns. Applying D-serine to lesioned larvae partially restored the flexible motor pattern indicating that excitatory synaptic activity is essential for a flexible pattern.
Using whole-cell current clamp recordings we found that larval excitatory descending interneuron, which provides the excitatory drive for swimming, persisted to fire once per swim cycle like its embryonic counterpart regardless of swimming frequency change. However, all other neurons, including inhibitory interneurons and motoneurons, were recruited or fire more action potentials during increase of swim frequency. Voltage clamp recordings have further shown that both excitatory and inhibitory post synaptic currents (PSCs) were enhanced in PSC

number and amplitude during high frequency swimming and decreased during slow swimming. However, the glycine receptor antagonist, strychnine (0.5 µM), did not affect flexible swimming pattern, despite the decrease in glycinergic inhibition and swim episode duration. Thus, the excitatory transmission seems play a more important role in swim frequency control, and the importance of the balance between excitation and inhibition needs to be further tested.
Reference: Issberner & Sillar. 2007. Eur J Neurosci, 26: 2256.

Disclosures: F. Jacquot: None. **H. Zhang:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.13/GG18

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Alfred Dunhill Links Foundation

Title: Cholinergic modulation of spinal motoneurons and locomotor control networks in mice

Authors: F. NASCIMENTO, L. R. B. SPINDLER, *G. B. MILES
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Abstract: Acetylcholine (ACh) is an intrinsic neuromodulator which fine-tunes neuronal function to allow adaptability of spinal motor output. The best described cholinergic modulatory system in the mammalian spinal cord involves C bouton synapses on motoneurons (MNs), which originate from cholinergic interneurons (INs) expressing the transcription factor Pitx2 (Zagoraiou et al., Neuron, 2009). Although indirect evidence suggests C boutons modulate MN output via activation of M2 receptors (Miles et al., PNAS, 2007), locomotor-related MN output can be modulated via M2 and M3 receptors (Jordan et al., Front Neural Circuits, 2014). Thus, further research is required to decipher the multiple mechanisms by which ACh may modulate spinal circuits. We first investigated the consequences of activation of muscarinic receptor subtypes (M2 and M3) using whole-cell patch-clamp recordings of MNs in spinal cord slices from neonatal mice (postnatal day (P)0-10). Application of muscarine (10µM) had an initial excitatory, followed by a delayed inhibitory effect on the frequency and amplitude of mixed post-synaptic currents (PSCs). Muscarine also increased MN firing frequency and elicited a depolarizing current in a subset of larger MNs, while inducing a hyperpolarizing current in a group of smaller MNs. The M2 antagonist methoctramine (10µM) blocked the hyperpolarizing current, delayed decrease in PSCs and increase in firing output induced by muscarine. The M3 antagonist 4-DAMP (2µM) blocked the depolarizing current and initial increase in PSCs induced by muscarine. We next investigated the role of M2 and M3 receptors in the modulation of drug-induced (NMDA 5 µM, 5-HT 10 µM and DA 50µM) locomotor-related MN output recorded

from ventral roots and individual MNs in spinal cord preparations from P0-5 mice. Blockade of M2 receptors (methoctramine; 10µM) decreased the amplitude of ventral root bursts and reduced the firing of individual MNs. In contrast, the M3 antagonist (4-DAMP; 2µM) destabilised the locomotor rhythm. Next, to directly investigate the effects of activating Pitx2+ INs, we used Pitx2::Cre:CHRM3 DREADD mice in which Pitx2+ INs were activated by administration of CNO (500nM-10µM). Recordings from MNs in whole spinal cord preparations demonstrated that activation of Pitx2+ INs led to an increase in MN firing frequency. We are currently assessing which muscarinic receptor subtypes (M2 vs M3) underlie these effects of Pitx2+ INs on MNs. Taken together, our data reveal differential roles for M2 and M3 muscarinic receptors in the modulation of mammalian spinal MNs and locomotor circuitry. We also provide the first direct evidence of modulation of MN output by Pitx2+ INs.

Disclosures: F. Nascimento: None. **L.R.B. Spindler:** None. **G.B. Miles:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.14/GG19

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01 NS066587

NIH Grant R01 NS070583

NIH Grant R01 MH051393

Title: Differential role of cerebral higher-order interneurons in the removal of default state inhibition and the generation of ingestive motor programs in *Aplysia*

Authors: *C. G. EVANS[1], J. JING[2,1], K. R. WEISS[1], E. CROPPER[1]
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Nanjing Univ., Jiangsu, China

Abstract: We study the default state and dynamic changes in a multi-functional network in the mollusc *Aplysia* that generates ingestive, egestive and intermediate motor programs. Previous experiments identified a command-like neuron (cerebral buccal interneuron 2 (CBI-2)) that can trigger ingestive motor programs. However, programs are only ingestive after CBI-2 is repeatedly stimulated (Proekt et al. 2004). When CBI-2 is initially activated programs are poorly defined (antagonistic motor neurons are coactive). These programs have 'intermediate' characteristics. As CBI-2 stimulation continues, however, the patterning of motor activity changes and programs become progressively more ingestive, (i.e. repetition priming occurs). Interestingly, we now show that in some preparations motor activity is not reconfigured and remains intermediate even with repeated CBI-2 stimulation. A question we address is, why does

reconfiguration fail? Previous work has demonstrated that CBI-2 induced priming is to a large extent achieved by the removal of a default state-associated inhibition that involves a progressive reduction in the firing frequency of the inhibitory interneurons B4/5 (Dacks et al. 2012). We hypothesized that in preparations in which CBI-2 induced priming is not observed the default state inhibition is not removed. Consistent with this idea we show that there is a correlation between B4/5 firing frequency and the ability of the preparation to undergo priming. Other experiments focused on the role of two other CBIs that like CBI-2, are activated by food. One, CBI-3, inhibits B4/5. The other, CBI-12, does not. We conducted experiments in preparations in which ingestive motor programs cannot be induced by repeated activation of CBI-2 and sought to determine whether it is observed if CBI-2 is coactivated with either CBI-3 or CBI-12. We found that intermediate programs were converted to ingestive with co-activation of CBI-3 (which inhibits B4/5) but were not converted by coactivation of CBI-12 (which does not inhibit B4/5). Interestingly, when ingestive activity was induced by CBI-2/3 coactivation, programs were immediately ingestive, i.e., repetition priming was not necessary. Taken together with previous work this suggests that when CBI-2 is stimulated on its own, successful priming requires removal of default state inhibition. Consequently there is a gradual transition between intermediate and ingestive activity. In contrast, when CBI-2 and CBI-3 are coactivated, priming is no longer necessary for the removal of default state inhibition. Consequently ingestive activity can be triggered without the slow dynamics observed when CBI-2 is stimulated on its own.

Disclosures: C.G. Evans: None. **J. Jing:** None. **K.R. Weiss:** None. **E. Cropper:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.15/GG20

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CIHR

NSERC

Title: Chemogenetic activation of parapyramidal brainstem neurons to evaluate motor consequences

Authors: *K. E. ARMSTRONG[1], M. NAZZAL[2], X. CHEN[3], K. STECINA[3], L. M. JORDAN[4]
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Abstract: Purpose: Several brainstem regions are necessary to provide transmission of a descending signal to motor networks within the lower limbs. The parapyramidal region (PPR) appears to play an important role in the transmission of a descending signal in the neonatal rat. However, the importance of this region in adult rats has not been studied in detail. The recent advent of DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) has allowed for non-invasive in vivo manipulation of neurons. Using DREADDs, the PPR can be selectively activated its designer drug, clozapine-n-oxide (CNO) to investigate its role in motor activity. **Methods:** DREADDs were stereotaxically injected in the PPR using adeno-associated viral vectors - AAV-hSyn-DIO-hM3Dq (mutated human muscarinic G-protein coupled receptor-Gq) with an m-Cherry reporter protein. After a recovery period to allow transfection, rats were tested in both voluntary (open field) and fictive locomotion to evaluate motor activation after administration of CNO**.** In acute experiments, rodents received surgery under isoflurane anesthesia to allow for recording of electroneurograms (ENGs of the tibial (Tib) and the common peroneal (CP) nerves). The preparation was decerebrated to permit the study of direct effects of PPR neurons without contribution of higher brain centers. To reliably evoke fictive locomotion, metal electrodes were stereotaxically targeted in the MLR for electrical stimulation (10-100 μA, 10-40 Hz). **Results:** Immunohistochemical detection and fluorescence microscopy revealed the presence mCherry protein within the PPR, providing evidence for the feasibility of transfection of these rodents with the selected AAV viral vector. Open field showed increased instances of freezing and grooming after CNO. Locomotor parameters did not change significantly after CNO compared to saline injected controls. In acute experiments, changes were observed in MLR-induced fictive locomotion and spontaneous ENG activity. In four animals, there was an increase in ENG activity occurring between 3-20 minutes after CNO injection (1 mg/kg). These effects decreased, and a recovery condition similar to control was observed after 40 minutes. **Conclusions:** DREADDs were successfully transfected within the PPR and confirmed by the presence of the mCherry reporter. Activation of these neurons was inconclusive in open field measures but may be due to confounding effects from higher brain centers. The acute decerebrate experiment demonstrates that DREADD activation of the PPR increases MLR-induced activity and spontaneous activity in all nerves recorded.

Disclosures: K.E. Armstrong: A. Employment/Salary (full or part-time):; University of Manitoba. **M. Nazzal:** A. Employment/Salary (full or part-time):; University of Manitoba. **X. Chen:** A. Employment/Salary (full or part-time):; University of Manitoba. **K. Stecina:** A. Employment/Salary (full or part-time):; University of Manitoba. **L.M. Jordan:** A. Employment/Salary (full or part-time):; University of Manitoba.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.16/GG21

Topic: E.07. Rhythmic Motor Pattern Generation

Support: ERC Advanced Grant: Locomotor Integration

Swedish Research Counsil

Hjärnfonden

Stratneuro

Title: Excitatory signal from brainstem neurons that initiates locomotion

Authors: *L.-J. HSU, O. KIEHN
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Abstract: Locomotor-initiating signals from the midbrain are funneled through neurons in the reticular brainstem formation to reach the spinal locomotor circuits. The aim of this study is to identify the brainstem neurons forming the final command signal that initiates over-ground locomotion with the ultimate aim of identifying the mechanism for how spinal locomotor circuits are activated from the brainstem. For this we have used detailed mapping of locomotor-initiating areas in the pons and hindbrain using an *in vitro* brainstem-spinal cord preparation of neonatal mice. We find a restricted area in the caudal-half of the brainstem, with sharp mediolateral boundaries where low threshold unilateral electrical stimulation evokes coordinated locomotor-like activity which resembles locomotor behaviors observed in vivo. The locomotor frequency is modulated with the frequency of electrical stimulation (ES) and generally faster than that evoked by drug-application to the spinal cord. Optogenetic experiments show that activation of glutamatergic neurons in the ES-defined area evokes locomotor-like activity similar to the ES-evoked one, suggesting that glutamatergic neurons are involved. When glutamatergic transmission is blocked in the brainstem, the cervical, and thoracic spinal cord, both optogenetic and electrical stimulation still evokes locomotor-activity in the lumbar spinal cord. These results suggest that excitatory reticulospinal neurons can activate the locomotor networks in the lumbar spinal cord directly to initiate locomotion. Our study localizes an initiating signal to a restricted area of the brainstem and provides means to functionally define the cellular targets of this descending signal in the spinal locomotor networks.

Disclosures: L. Hsu: None. **O. Kiehn:** None.

Poster

065. CPGs: Neuromodulation, Sensory Input, and Descending Control

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 065.17/GG22

Topic: B.09. Physiological Properties of Neurons

Support: NSF IOS 1354932

Title: Frequency dependent modulation of stimulus encoding by antidromic action potentials

Authors: *M. DEMAEGD, W. STEIN
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Abstract: Neurons encode dendritic stimuli via the number, frequency, and precise timing of action potentials (APs) at their spike initiation zone. Stimulus encoding depends on many factors, including membrane excitability. Excitability, however, changes in the presence of APs, and may thus be affected by antidromic signals reaching the stimulus-encoding areas of the neuron. Ectopic APs, for example, can be generated in the axon trunk and travel antidromically towards the axon origin and the primary site of spike initiation (Pinault, 1995 Brain Res). Pathological conditions, modulatory and synaptic inputs, and physician-induced stimuli can elicit these ectopic APs (Arbuthnott et al, 2007, J Neurophysiol). The effects of antidromic APs on stimulus encoding at the primary site of spike initiation, however, remain poorly understood. We hypothesize that antidromic APs invade the site of spike initiation and alter stimulus encoding in a frequency-dependent manner, such that the number and frequency of orthodromic APs changes. To test this hypothesis, we utilize a combination of electrophysiology and computer modeling of the anterior gastric receptor neuron (AGR) in the crab, *Cancer borealis*. AGR is a single-cell muscle tendon organ in the experimentally advantageous crustacean stomatogastric nervous system. Its axon is several cm long and ectopic APs are generated spontaneously in its axon trunk, in addition to sensory APs that are initiated at its primary spike initiation site near the peripheral dendrites. The biogenic amines, Octopamine and Histamine, and the peptide transmitter, FLRFamide, differentially modulate AGR’s ectopic spike frequency (Städele & Stein, 2016, J Neurosci; Städele & Stein, 2015, bioRxiv). To test the effects of changing ectopic spike frequencies, we elicited peripheral bursts at AGR's sensory spike initiation zone, and stimulated antidromic APs at different frequencies. Ectopic spikes invaded the sensory spike initiation zone, where they caused three distinct frequency-dependent actions on sensory encoding: 1) reduction of the number of orthodromic APs, 2) alteration of orthodromic spike timing, and 3) reduction of orthodromic spike frequency in response to peripheral stimuli. Thus, modulation of AGR's ectopic spike frequency in the axon trunk altered information encoding at the primary spike initiation site. Our computer model of a generic Hodgkin-Huxley axon predicts that these responses are due to excitability changes caused in the wake of antidromic APs. Hence, pathological, modulatory, or externally-induced ectopic APs not only add to the output of neurons, but also alter stimulus encoding in a frequency-dependent manner.

Disclosures: **M. Demaegd:** None. **W. Stein:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.01/GG23

Topic: F.01. Neuroethology

Support: Simons Award 365000

Title: Characterization of neuronal dynamics in a variability generating circuit

Authors: *G. F. LYNCH[1], H. S. SOHAL[3], E. S. BOYDEN[2], M. S. FEE[4]
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Abstract: Many behaviors are acquired through trial and error. Consistent with reinforcement learning, animals explore a behavioral space, evaluate the outcomes of their actions, and modify their behavior based on the outcomes. While a large number of studies have explored the neural basis of evaluation signals (Schultz et al. 1997) and the modification of behavior based on past rewards (Hikosaka 2007), much less is known about the neural activity driving exploratory behavior. In most species, the source of this exploratory variability is unknown, but in songbirds vocal variability is generated by a neural circuit that includes the premotor cortical region LMAN (Kao et al. 2005). Furthermore, this variability-generating circuit is required for song learning (Bottjer et al. 1984). In order to understand how neural activity in LMAN generates behavioral variability, here we study the population activity of LMAN in juvenile zebra finches as they sing highly variable song.
To simultaneously record from a large number of neurons in singing juvenile birds, we developed a miniaturized microdrive capable of recording from 64 extracellular electrodes. To characterize the spatial structure of LMAN population activity, we additionally developed a high-density 4 x 16 array of flexible electrodes whose position we can adjust to isolate single neurons in singing birds. These technologies have allowed us to make population recordings in singing juvenile zebra finches during the developmental stages when their song is largely driven by LMAN activity. By simultaneously recording from a number of neurons in singing juvenile birds, we can characterize the statistics and patterns of population activity within single song renditions.

Disclosures: G.F. Lynch: None. **H.S. Sohal:** None. **E.S. Boyden:** None. **M.S. Fee:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.02/GG24

Topic: F.01. Neuroethology

Support: NIH Grant 5-RO1-DC009183-03

Title: Quantification of single unit activity related to head and body movements in the intermediate arcopallium of the zebra finch

Authors: *M. E. STETNER[1], M. S. FEE[2]
[1]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [2]Brain & Cog Sci. / McGovern Inst., Massachusetts Inst. Tech., Cambridge, MA

Abstract: Songbird brain areas controlling vocal production and learning are segregated into a set of distinct nuclei. Surrounding this vocal motor network is a parallel set of brain areas including lateral intermediate arcopallium (LAI) which is adjacent to the song motor nucleus RA. In this second circuit, brain areas have connections similar to the vocal network. The similarity in the anatomy of these networks suggest that they may also share a common function. There are two competing hypotheses for the role of this parallel pathway. Under one hypothesis, it is involved in song learning (Bottjer and Altenau 2010). Even though it is not required for vocal production, it might contribute to learning by carrying information about vocal errors. In support of this hypothesis, in young birds under anesthesia, the parallel circuit responds to playback of the tutor song (Achiro and Bottjer 2013). In an alternative hypothesis, the parallel network is involved in non-song motor control. Just as the adjacent song network controls the muscles of the syrinx, the parallel network could control the other muscles of the head and body. Consistent with this motor hypothesis, the midbrain motor centers that control these body muscles receive input from LAI via the OM tract (Bottjer et al. 2000), and the parallel network exhibits increased immediate early gene expression following hopping, but not singing (Feenders et al. 2008).
To distinguish these hypotheses, we made single unit recordings in LAI in awake freely behaving male zebra finches. In our initial recordings, we found that LAI neurons did not respond to vocal errors during singing. However, they did respond to head turns, grooming and chewing motions that we identified by hand from video recordings.
To quantify the birds' motion, we designed a new motorized microdrive with an integrated gyroscope, accelerometer, and compass. For some birds, an additional gyroscope, accelerometer, and compass were placed on the body as well. Single unit activity and head and body orientations and were recorded simultaneously as birds moved freely in their cages. Their motion was segmented into discrete movements and classified. Single units in LAI change their firing

rate with specific movement types. These changes begin before movement onset, which is consistent with a premotor role.

Disclosures: **M.E. Stetner:** None. **M.S. Fee:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: F.01. Neuroethology

Support: NDSEG graduate fellowship

Mathers Foundation Grant 024094-001

NIH Grant 5-RO1-DC009183-03

Simons Award 365000

Title: Neural sequences underlying the rapid learning of new syllables in juvenile zebra finches

Authors: *E. L. MACKEVICIUS[1], N. DENISSENKO[2], M. S. FEE[3]
[1]MIT, Cambridge, MA; [2]Brain & Cog Sci. / McGovern Inst., Massachusetts Inst. Technol., Cambridge, MA; [3]Brain & Cog Sci. / McGovern Inst., Massachusetts Inst. Tech., Cambridge, MA

Abstract: How do song sequences emerge over development? Young songbirds babble (subsong), then develop a repeatable 'protosyllable', which differentiates and matures into new syllable types that are refined to match the song of a tutor bird (Tchernichovski et al 2001). Underlying this process are neural sequences in the premotor area HVC. The HVC neural population initially assembles a protosyllable sequence, which then splits into 'daughter' sequences in a process similar to gene duplication (Okubo et al. 2015).
Previous studies of this process could only track changes in the neural population that occurred at a timescale slower than a week, because population statistics had to be compiled from single-neuron recordings, and only several neurons could be recorded per day due to the low yield of existing techniques. However, this process misses rapid song changes that can happen within a day, and correlate with changes in state of the song motor system (Tchernichovski et al. 2001, Shank and Margoliash 2009). We set out to address how the premotor area HVC gives rise to these rapid song changes.
We use a miniaturized microscope (Inscopix) in combination with training protocols to adapt young birds to sing with the microscope attached. We have found that the activity-dependent calcium indicator GCaMP6f provides sufficient temporal resolution to resolve the faster

rhythmic bursting in HVC in juvenile birds. We have recorded from large populations of neurons in 5 singing juvenile birds through several weeks of song development, and are analyzing patterns of activity to identify underlying modes of network dynamics. This has allowed us to observe, at a moment-to-moment timescale, how neural ensembles are flexibly formed and recruited to generate rapid changes in the song.

Disclosures: E.L. Mackevicius: None. **N. Denissenko:** None. **M.S. Fee:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

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Program#/Poster#: 066.04/GG26

Topic: F.01. Neuroethology

Support: NSF Grant IOS-1456965

NSF Grant IOS-1656360

Title: Auditory experience changes neuronal intrinsic physiology

Authors: *M. T. ROSS[1], D. FLORES[2], R. BERTRAM[2], F. JOHNSON[1], R. L. HYSON[1]
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Abstract: The learned vocalizations of songbirds are acquired over sensory and sensorimotor stages of learning. During the sensory stage of learning, an auditory memory of the tutor's vocal pattern is encoded. It is known that the cortical premotor nucleus HVC is important for the auditory encoding of tutor song and the eventual production of learned vocalizations. We have previously shown developmental changes in the intrinsic physiology of HVC neurons that coincide with stages of song learning, however it was unknown if auditory experience was driving those changes. To determine if auditory experience was driving intrinsic changes in HVC neurons, we compared neurons from birds with varying durations of exposure to the tutor's song. Patch clamp experiments compared the intrinsic physiology of HVC neurons in juvenile birds with no tutor exposure, birds with between 1-10 days of exposure, and control birds with continual exposure (~30 days). Additionally, we developed biophysical models of the intrinsic physiology of HVC neurons to predict which changes in ion channel expression are shaped by auditory experience. The results suggest that auditory experience does drive the changes in intrinsic physiology observed in HVC neurons over development. Some observations included alterations in the response of HVC_X neurons to hyperpolarizing current pulses, including model-predicted changes in the I_h current and the T-type Ca^{2+} current. Additional changes included a shift in the resting potential of HVC_{RA} neurons. These findings suggest that vocal-motor learning involves not only the alteration of synaptic weighting between neurons, but also changes in the

intrinsic physiology of the component neurons in the circuit. Consequently, models of vocal learning should account for these intrinsic changes along with changes in synaptic connectivity. More broadly, models of learning and memory should consider intrinsic plasticity of neurons as a possible contributor to how the nervous system encodes new information or novel behaviors.

Disclosures: **M.T. Ross:** None. **D. Flores:** None. **R. Bertram:** None. **F. Johnson:** None. **R.L. Hyson:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.05/GG27

Topic: F.01. Neuroethology

Support: NSF IOS 1456965

Title: Syllable sequence variability in a distributed network model for the control of singing in songbirds

Authors: ***D. GALVIS**[1], W. WU[2], R. L. HYSON[3], F. JOHNSON[3], R. BERTRAM[4]
[1]Mathematics Dept., Florida State Univ. Dept. of Mathematics, Tallahassee, FL; [2]Statistics Deptartment, [3]Psychology Dept., [4]Mathematics Dept., Florida State Univ., Tallahassee, FL

Abstract: Male zebra finches produce a canonical sequence of discrete song units called syllables that are separated by short silent phases. Although the premotor nucleus HVC (proper name) is responsible for much of the temporal coding of learned song in the birds, a growing body of evidence suggests that a distributed network including cortical, thalamic, and brainstem nuclei contribute to song timing. We recently published a distributed neural network model for the production of birdsong that also accounts for the discrepant effects of bilateral ablations of medial or lateral portions of HVC. Here, we describe a simplified version of this model that replaces biophysical neurons with simple binary units, while preserving the connectivity of the original model. Replacing conductance-based neurons with phenomenological representations of their behavior allows us to focus on the signaling properties of the neural architecture specifically. We use this simplified model to explore sources of sequence variability that are characteristic of other bird species, such as the Bengalese finch. We consider various adaptations to the architecture of our model focusing on the statistical properties of the output syllable sequence. We find that small changes to the internuclear connectivity schemes add variability to the original song structure, with statistical characteristics relevant to the songs of other birds. Consequently, this model makes predictions about relatively subtle species-specific variations in neural connectivity that could account for the differences in song sequence stereotypy.

Disclosures: **D. Galvis:** None. **W. Wu:** None. **R.L. Hyson:** None. **F. Johnson:** None. **R. Bertram:** None.

Poster

066. Vocal Learning Across Avian Models

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.06/GG28

Topic: F.01. Neuroethology

Support: NSF IOS-1456965

Title: Graceful degradation of song following progressive ablation of songbird vocal-premotor cortex

Authors: *D. W. SHAUGHNESSY[1], R. BERTRAM[2], W. WU[3], R. L. HYSON[1], F. JOHNSON[1]
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Abstract: The learned adult song of male zebra finches is encoded by neural activity in a premotor region of avian cortex (HVC, proper name). Learned songs are typically ~1sec in duration and consist of a discrete set of syllables (which can vary in duration and spectral complexity) produced in a canonical sequence. Syllables are separated by small gaps of silence that distinguish one syllable from another. Recordings of individual HVC neurons in singing birds suggest that songs are encoded in continuous time (Lynch et al. 2016; Picardo et al. 2016) or as a set of temporally-discontinuous sub-syllabic gestures (Amador et al. 2011; Boari et al. 2015). Ablation findings suggest another possibility - encoding occurs at the whole syllable level, with song syllables and their canonical sequence encoded in parallel, by lateral and medial HVC, respectively (Basista et al. 2014). Recent modeling work (Galvis et al. 2017) proposes that medial HVC determines the syllable sequence by controlling termination of inter-syllable gaps and the initiation of the next syllable in the sequence. Here, we apply a progressive ablation strategy to medial HVC to determine whether larger ablations can cause the sequencing of whole syllables to divide or break into smaller temporal or gestural units of song. With increasingly large ablation of medial HVC, preliminary data show deterioration of song consistent with the network property of graceful degradation, which is expected given the massively parallel connectivity of HVC (Elliott et al., 2017). That is, like birds with smaller medial HVC ablations (Basista et al. 2014), all pre-operative syllables are often produced in their canonical sequence. However, in other instances of singing, individual syllables break down and are sung in smaller ~60msec units, separated by discrete gaps of silence. These vocalizations appear to be syllable fragments because their spectral structures align to different portions of individual pre-operative syllables. The unitary duration of the sub-syllabic elements is striking, raising the possibility that each whole syllable is composed of a number of smaller temporal or gestural units, and that medial HVC plays a role in sequencing these units to produce whole syllables.

Disclosures: **D.W. Shaughnessy:** None. **R. Bertram:** None. **W. Wu:** None. **R.L. Hyson:** None. **F. Johnson:** None.

Poster

066. Vocal Learning Across Avian Models

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Topic: F.01. Neuroethology

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Title: Left-lateralized brain activity is necessary for vocal learning in zebra finches

Authors: A. H. PAGLIARO, H. C. PIRISTINE, J. S. LORD, *S. M. H. GOBES
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Abstract: In humans and songbirds, neuronal activation for language and song shifts from bilateral- or diffuse-activation to left-hemispheric dominance with increasing proficiency (Moorman et al., 2012, Chirathivat et al., 2015, Holland et al., 2015). Further parallels exist at the behavioral level: unstructured juvenile vocalizations become highly stereotyped adult vocalizations through a process of trial and error learning. Greater left-hemispheric dominance in the songbird caudomedial Nidopallium (NCM), a Wernicke-like region, is related to better imitation of the tutor's song learned early in development, indicating a role for left NCM in forming auditory memories (Moorman et al., 2012). Here, we hypothesize that inhibition of the left NCM during interaction with a song tutor would impair imitation of the tutor's song more than inhibition of the right NCM. We infused a transient sodium channel blocker (TTX) immediately prior to tutoring sessions in either left or right NCM of previously isolated juvenile male zebra finches (*Taeniopygia guttata*). Upon maturation, we assessed imitation success by comparing the acoustic features of the songs of the experimental birds to their tutors' songs. Additionally, we analyzed the temporal structure of each bird's adult song to evaluate its rhythmic complexity. We found that right-infused birds had imitated their tutor's song to some degree, but learning in left-infused birds was significantly impaired (paired t-test for tutor versus novel song similarity: left-TTX $t(5) = 3.22$, p = n.s.; right-TTX $t(6) = 4.93$, $p = 0.003$. The songs of the left-infused birds also showed significantly less rhythmic complexity (independent t-test

left vs. control: $t(12) = -2.64$, $p = 0.021$). Taken together, these results suggest that activity in the left NCM is critical for successful song learning. As bilateral or right-lateralized activity is a characteristic of many human speech disorders, these findings in birds reveal the underlying mechanism: predominant activity in the left hemisphere during formation of perceptual memories is a prerequisite for successful skill development.

Disclosures: **A.H. Pagliaro:** None. **H.C. Piristine:** None. **J.S. Lord:** None. **S.M.H. Gobes:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.08/GG30

Topic: F.01. Neuroethology

Support: JSPS KAKENHI grant #17H05754 to Y.Y-S.

KAKENHI Incentive Program #10Y60IC001 to T.K.

Title: Early auditory experience modifies neuronal firing properties in zebra finch auditory cortex

Authors: *T. KUDO, Y. YAZAKI-SUGIYAMA
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Abstract: Juvenile male zebra finches learn to sing based on early auditory experiences with adult tutors during a limited developmental time window, called the critical period. They first hear and memorize tutor songs (normally their fathers') during a sensory learning period, and then match their own vocalizations to the memorized songs using auditory feedback. We recently reported that early tutor song experiences shape neuronal auditory responsiveness in the caudomedial nidopallium (NCM), homologous to the mammalian higher auditory cortex (Yanagihara and Yazaki-Sugiyama, 2016). To identify the neuronal mechanism of the sensory learning critical period, we examined development of neurophysiological properties of NCM neurons with tutor song experience during the sensory learning period (20, 40, and 60 days-post-hatching [DPH]) in male and female juveniles using whole-cell patch clamp recordings *in vitro*. We found three types of neurons in the NCM with distinct spontaneous firing rates: silent, low frequency (< 9 Hz), and high frequency (> 9 Hz) neurons. The proportion of low-frequency neurons increased in both males and females from 20 to 40 DPH during the male sensory learning period, and then decreased by 60 DPH when the sensory learning period is over. Some low- and high-frequency neurons showed tonic bursts during spontaneous firing (burst-type neurons) in both sexes, the percentage of which also increased by 40 DPH, and then returned to

the 20 DPH level by 60 DPH in both sexes. In contrast, in male juveniles that were isolated from their fathers starting at 10 DPH to examine the effects of tutor song experience, the proportion of low-frequency neurons gradually increased from 40 to 80 DPH. Isolated male juveniles also showed a gradual increase in the proportion of burst-type neurons from 40 to 80 DPH. In females, which do not learn to sing, those effects of isolation were not observed. These results imply that auditory isolation from a tutor, which delays the closing of the sensory learning period, also delays development of NCM neurophysiological properties. These findings suggest that early tutor song experience modifies NCM neurophysiological properties, especially firing properties that may enable song memory formation.

Disclosures: T. Kudo: None. **Y. Yazaki-Sugiyama:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.09/GG31

Topic: F.01. Neuroethology

Support: NSF IOS-1354962

Helen Hay Whitney Postdoctoral Fellowship

Title: Representation of self-generated vocalizations and vocal models in the songbird brain

Authors: *M. BEN-TOV, M. G. KEARNEY, S. PETERS, S. NOWICKI, R. D. MOONEY
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Abstract: Many of our most complex behaviors, including speech and music, are learned by imitation. To learn to imitate a suitable model, we form sensory representations of our tutor's actions, which we then use to build motor programs that encode the imitative skills. Similar to humans, the song sparrow, a wild songbird species, learn their songs by imitating songs of suitable tutors. Juvenile song sparrows can memorize many different tutor songs and then many months later learn to sing precise copies of these songs, indicating that auditory experience of tutor songs leads to the formation of long-lasting auditory memories in the pupil's brain. Our goal is to understand how these long lasting auditory memories are stored in the song sparrow's brain. The sparrows in our experiments were tape-tutored with multiple tutor songs as juveniles and then raised in acoustic isolation up until adulthood. We then used viral expression of GCaMP6s in combination with in vivo multiphoton calcium imaging in anesthetized birds to explore the auditory responses of HVC neurons to the bird's own songs as well as its tutor songs. This approach allowed us to test whether representations of the bird's own songs and tutor songs are encoded by the same or different populations of neurons, and whether single neurons encode

such dual representations independent of whether the bird's own song that drives a response is a copy of the effective tutor song. We found neurons that strongly responded to at least one of the bird's own songs as well as other neurons that responded to a tutor song model but not to a copy of that model, suggesting that some HVC neurons encode an auditory memory of the tutor song. Future studies will use wide field imaging methods to determine whether these representations are also present in the awake, freely behaving bird and to explore the possible correspondence between auditory and motor representations of song in the song sparrow's HVC.

Disclosures: M. Ben-Tov: None. **M.G. Kearney:** None. **S. Peters:** None. **S. Nowicki:** None. **R.D. Mooney:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

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Program#/Poster#: 066.10/GG32

Topic: F.01. Neuroethology

Support: NSF GRFP

Title: The effects of phasic excitability on neural selectivity and tolerance for zebra finch song

Authors: *M. BJORING, C. D. MELIZA
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Abstract: Birdsong is a complex vocalization that bears important similarities to human speech. Critical to recognizing speech or birdsong is the ability to discriminate between similar sequences of sound that may carry different meanings. The caudal mesopallium (CM) is a secondary area in the auditory system of songbirds that is a potential site for song identification, displaying both between-category selectivity and within-category tolerance to conspecific song. Electrophysiological studies of CM have identified a population of neurons with intrinsically phasic firing patterns in addition to the more typical tonic and fast-spiking neurons. The function of these phasic neurons in processing spectrotemporally complex conspecific vocalizations is not known. We investigated the auditory response properties of phasic and tonic neurons using computational modeling and in vivo electrophysiological approaches with particular focus on the selectivity and entropy of the neural responses to birdsong. When biophysical models of phasic and tonic neurons were presented with identical inputs, the phasic models were more selective among syllables and more robust to noise-induced variability, potentially providing an advantage for identifying songs in noisy listening conditions. Using whole-cell in vivo recordings in sleeping zebra finches, we tested the model predictions that a higher degree of intrinsic phasicness is correlated with greater selectivity and lower noise entropy in the response to song.

Disclosures: **M. Bjoring:** None. **C.D. Meliza:** None.

Poster

066. Vocal Learning Across Avian Models

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Program#/Poster#: 066.11/GG33

Topic: F.01. Neuroethology

Support: NSF Grant IOS 1456356

Title: Spontaneously firing neurons in hummingbird vocal control nucleus VA, analogous to songbird RA

Authors: ***D. J. PERKEL**[1], C. A. WILLIAMS[2], K. E. MILLER[3], P. V. LOVELL[4], C. V. MELLO[4]
[1]Depts. Biol. & Otolaryngology, [2]Dept. Biol., [3]Dept. Otolaryngology, Univ. of Washington, Seattle, WA; [4]Dept. of Behavioral Neurosci., Oregon Hlth. and Sci. Univ. Sch. of Med., Portland, OR

Abstract: Vocal learning has evolved in three bird lineages, namely songbirds, parrots and hummingbirds. In songbirds and parrots, a specific set of interconnected forebrain nuclei show specialized molecular and electrophysiological features that presumably underlie the learning and production of rapid, temporally precise movements needed to produce learned vocalizations. For example, the songbird robust nucleus of the arcopallium (RA) has projection neurons that are intrinsically spontaneously active, a property rare in pallial regions of the mammal or avian brain. In hummingbirds, an avian lineage that evolved independently from songbirds and parrots, the vocal nucleus of the arcopallium (VA) is thought to be analogous to songbird RA because of cytoarchitectonic similarity, immediate early gene expression during vocalization and preliminary data that it projects to brainstem motor and premotor neurons for vocalization. VA also shows molecular specializations shared with songbird RA. Here we hypothesized that VA neurons would also exhibit one of the key distinguishing features of RA neurons, presumable specializations for rapid, precisely timed firing during song production.
We prepared brain slices from adult male Anna's hummingbirds (*Calypte anna*), an established vocal learner species, and made extracellular single-unit or whole-cell recordings from neurons in nucleus VA. We observed that over half (13 of 24) of neurons recorded in VA showed spontaneous activity (range 1-8 Hz). These neurons also showed other features that made them resemble RA neurons, including a linear increase in firing rate with increasing depolarizing current injection and moderate sag upon hyperpolarization, consistent with moderate expression of hyperpolarization-activation cation conductance. Neurons in the arcopallium but outside VA showed a lower prevalence of spontaneous firing (3 of 10).
We also assessed myelination using a silver stain. The putative nuclei of the motor pathway, the

vocal nucleus of the lateral nidopallium (VLN) and VA, showed a high degree of myelination overall, mediated by a dense plexus of branched myelinated axons. This resembles the myelination of HVC and RA in songbirds, and is consistent with a specialization for rapid and precise action potential conduction along axons.
Together, these data suggest that, accompanying the evolution of vocal learning in songbirds and hummingbirds, there was convergence towards similar firing and myelination specializations in the forebrain descending motor pathway for vocal production in these two separate taxa.

Disclosures: D.J. Perkel: None. **C.A. Williams:** None. **K.E. Miller:** None. **P.V. Lovell:** None. **C.V. Mello:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.12/HH1

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF

Title: Population activity in the song premotor nucleus RA exerts bidirectional control on pitch and amplitude of learned song syllables

Authors: *C. J. CHEUNG[1], M. N. MILLER[2], M. S. BRAINARD[3]
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Abstract: Nucleus RA (robust nucleus of the arcopallium) is a motor cortical analogue in the songbird forebrain that projects to brainstem vocal and respiratory musculature and is widely thought to participate in the moment-by-moment control of learned song features. Neural activity within RA is tightly coupled to the production of individual syllables (Yu and Margoliash 1996, Leonardo and Fee 2005), and variation in RA activity correlates with variation in learned song features such as syllable pitch and amplitude (Sober, Wohlgemuth and Brainard 2008). This suggests a model in which overall activity levels in RA specify the gain of upcoming vocal output, and bidirectional changes to the level of activity in RA should therefore drive concomitant bidirectional changes in the magnitude and direction of vocal behavior. We causally tested this model by using pharmacological manipulations of inhibition to bias the amount of activity in the RA microcircuit during song production. We found that suppressing RA inhibition produced robust and consistent increases in syllable pitch and amplitude. Conversely, increasing RA inhibition produced decreases in pitch and amplitude. These results are consistent with a model in which parametric modulation of the firing rate of RA projection neurons systematically biases highly calibrated vocal output, and suggest that the normally precise encoding of learned

acoustic features of song depends on the precise balance of excitation and inhibition acting on projection neurons within the RA microcircuit.

Disclosures: C.J. Cheung: None. **M.N. Miller:** None. **M.S. Brainard:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

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Program#/Poster#: 066.13/HH2

Topic: F.01. Neuroethology

Support: NIH Grant DC004722

Title: Regularities in zebra finch song beyond the repeated motif

Authors: *J. HYLAND BRUNO[1], O. TCHERNICHOVSKI[2]
[1]Psychology, [2]Dept. of Psychology, Hunter Col., New York, NY

Abstract: The proliferation of birdsong research into the neural mechanisms of vocal learning is indebted to the remarkable stereotypy of the zebra finch's song motif. Song motifs are composed of three to eight copied syllables, which birds learn to produce in a fixed order. But at a higher level of song organization - *the bout* - zebra finch song is no longer stereotyped. Song bouts include several repetitions of the motif which are often linked together by a variable number of calls. Here, we show that combinatorial analysis of motifs and connecting elements yields an incomplete description of bout structure. Presenting song bouts as sorted raster plots of acoustic features reveals additional structure in their temporal dynamics, with some motifs stringed together via tight connectors, and others via loose connectors. Loose connectors allow considerable timing variation across renditions. Even among birds that acquired the same motif, we observe strong variability in the temporal plasticity of song bouts. This holistic song feature represents a form of vocal flexibility, which may potentially be used for communication or vocal coordination.

Disclosures: J. Hyland Bruno: None. **O. Tchernichovski:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 066.14/HH3

Topic: F.01. Neuroethology

Support: HHF Grant 23103

Title: HVC damage reduces song stereotypy in adult male Bengalese finch song

Authors: *C. M. URBANO, C. FAVALORO, J. DUBOIS, M. WHITTINGTON, J. O. TAYLOR, B. G. COOPER
Dept. of Psychology, Texas Christian Univ., Fort Worth, TX

Abstract: Songbirds are an animal model for better understanding neural mechanisms underlying learned, sequential vocal behavior. Bengalese finches (*Lonchura striata domestica*) typically produce a song with a semi-variable repeated sequence of 8-12 syllables (i.e. acoustic elements). HVC (proper name) is a premotor area in the songbird brain that is critical for orchestrating species-typical song sequences. In this study, HVC was ablated in either the left or right hemisphere. We performed micro- (n = 8), macro- (n = 8), or sham (n = 5) lesions and quantified changes in the number of syllables post-lesion and transition entropy. Sham HVC lesion did not produce syntactic changes. In both the micro- and macro-lesion conditions, animals were evenly divided into left and a right HVC lesion groups. We did not find evidence for lateralization, therefore the data were pooled in subsequent analyses. In the microlesion group, we analyzed songs prior to, four and seven days post-surgery (PSD4, PSD7). Syllables were hand-coded and letters were used to give each syllable a unique identifier. In the micro-lesion group, novel syllables were observed after HVC lesion (post/pre ratio PSD4: 1.38 ± 0.18). Overall, the transition entropy increased by PSD4 (post/pre ratio: 1.54 ± 0.33), confirming HVC lesion reduces the stereotypy of song syntax. At PSD7, there was a decline in transition entropy (post/pre ratio: 1.18 ± 0.19). In the macro-lesion group, we recorded songs for up to five months post-surgery and selected songs at PSD7, one month and five months post-surgery (PSM1, PSM5). Similar to the micro-lesion group, we observed the addition of novel syllables and variable song syntax. Transition entropy increased at PSD7 (post/pre ratio: 1.72 ± 0.29) and syntax remained variable until PSM5 (post/pre ratio: 1.88 ± 0.57). The appearance of novel syllables would certainly explain the increase in transition entropy, however, we did not find that was always the case. In the microlesion condition at PSD4, the number of syllables accounted for 89% of the variance in transition entropy, and as the song recovers at PSD7, the number of syllables accounted for 42% of the variance in transition entropy. The opposite pattern was observed in the macrolesion group. At PSD7, the number of syllables produced by the macrolesion group accounted for 45% of the variance in transition entropy. At PSM1 and PSM5, there was no evidence of song recovery; at these timepoints, the number of syllables accounted for 97% and 96% of the variance in transition entropy. These results illustrate that HVC control of song syntax is not lateralized, and reveal different recovery patterns depending upon the extent of HVC damage.

Disclosures: C.M. Urbano: None. **C. Favaloro:** None. **J. DuBois:** None. **M. Whittington:** None. **J.O. Taylor:** None. **B.G. Cooper:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

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Topic: F.01. Neuroethology

Support: U.S. Dept. of Education Grant P200A150077

NIH/NIDCD Grant 1R01DC012859

ONR/BAA Grant 11004985

Title: Delayed auditory feedback in zebra finches rapidly induces changes in macro-scale song features

Authors: *G. FETTERMAN[1,2], D. MARGOLIASH[1,2,3]
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Abstract: How sensory feedback modifies motor actions, such as the action of auditory feedback in supporting moment-to-moment production and long term maintenance of learned vocalizations, remains an active area of research. Paralleling observations in humans, delayed auditory feedback (DAF) induces dramatic behavioral changes in zebra finches (Taeniopygia guttata) during singing, including dropped syllables and a stuttering-like behavior. Previous studies using DAF and other auditory feedback perturbations have only reported behavioral changes after relatively long periods of time - days to weeks of experimental treatment. We investigated the behavioral effects of DAF at shorter timescales - between 4 and 24 hours. Sensitive accelerometers were implanted onto the skulls of male zebra finches, allowing veridical recordings of singing via bone-conduction during continuous DAF (cDAF) perturbations. Recordings from 5 birds were manually labeled, with an eye towards structural features of song, including motifs (rigidly-determined sequences of syllables), bouts (motifs grouped closely in time, usually preceded by repeated introductory notes), and phrases (bouts grouped in time). Within the first four hours of exposure to cDAF, we observed several striking changes in singing behavior. Total singing decreased (but rebounded above pre-DAF baselines by the next morning). Phrases shortened, with the proportion of single-bout phrases rising dramatically. Bouts, however, lengthened, with the number of motifs per bout in some cases increasing by over 50%. Overall, motifs did not change significantly in numbers of syllables. However, bout-ending motifs were more likely to be sung to completion under DAF. The number of introductory notes preceding bouts rose under DAF, in some cases to values never seen in pre-DAF singing. These observations support a simple model for the initial effects of DAF on singing: the increase in motifs-per-bout and completion likelihood of bout-ending motifs suggest that motivation to sing is increased. The overall lower incidence of song, the increase in

the number of single-bout phrases, and the increased number of introductory notes before bouts further suggest that the birds find it difficult to begin singing and to maintain song once begun. Our results may be a behavioral manifestation of changes in intrinsic electrophysiological properties that have recently been observed in song system neurons projecting to the basal ganglia in birds exposed to short periods of cDAF.

Disclosures: G. Fetterman: None. **D. Margoliash:** None.

Poster

066. Vocal Learning Across Avian Models

Location: Halls A-C

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Topic: F.01. Neuroethology

Support: NIH Grant R01DC014364

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Klingenstein-Simons Fellowship

Title: Population calcium imaging of vocal-motor HVC neurons in singing birds

Authors: *V. K. DALIPARTHI, T. F. ROBERTS
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Abstract: Skilled behaviors often rely on the precise sequential production of a number of smaller individually controlled movements. Understanding how complex sequential behaviors are encoded by premotor neural circuits is an enduring challenge. Birdsong provides the best-studied example of a naturally learned and precisely timed sequential motor behavior. Male zebra finches for example sing a single courtship song comprised of multiple syllables repeated in a semi-stereotyped fashion to attract female birds. The core set of repeated syllables in a zebra finch song is referred to as a motif. While singing to a female, male zebra finches string together several motifs into a song bout. Production of this song bout is controlled by a well-delineated cortical circuit, providing an entry point for studying how skilled motor behaviors are encoded in the brain. The song premotor cortical nucleus HVC is necessary for singing and song learning, and is thought to control temporal sequencing of movements associated with singing. HVC contains at least three distinct classes of projection neurons, only one of which is acutely necessary for song production. Understanding how birdsong is encoded at the level of HVC would benefit from methods for monitoring the activity of distinct cell types within HVC during natural performance of courtship song. We have developed viral methods for labeling and

imaging only the vocal premotor neurons in the HVC of freely singing birds. Using a head-mountable miniaturized fluorescent microscope, we have performed calcium imaging from populations of vocal premotor neurons in adult zebra finches singing their courtship song to female birds. Using these methods we have begun to study how song bouts are encoded in HVC by differing spatial and temporal patterns of activity. This research provides new avenues for examining how populations of identified neurons in HVC encode behavior and for studying the functional organization of HVC.

Disclosures: V.K. Daliparthi: None. **T.F. Roberts:** None.

Poster

066. Vocal Learning Across Avian Models

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Topic: F.01. Neuroethology

Support: NIH Grant NS089679

NIH Grant NS098536

Title: Calcium signals of order, syntax, and action in canary (serinus canaria) HVC

Authors: *Y. COHEN, J. SHEN, D. SEMU, D. P. LEMAN, W. A. LIBERTI, N. L. PERKINS, T. J. GARDNER
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Abstract: Interaction with the world requires control of sequential movements in real time. Often, a motor skill relies on flexible composition of basic elements using long-range syntactic rules. Despite findings of single-neuron and network correlates of motor sequence and timing, the neural mechanisms underlying behavior with flexible long-range structure are largely unknown.
Songbirds have a learned and highly reliable behavior – song, whose temporal structure is largely governed by activity of the premotor nucleus HVC (Hahnloser and Fee 2002, Long and Fee 2008, Wang 2008, Nottebohm 1976). In zebra finches, the fixed motifs and the syllables' timescales, which are very close to the neural timescales (Markowitz 2015), prevent a clear distinction between neural coding of timing and sequencing of song elements. Bengalese finches variably transition between syllables and create short phrases of repeated syllables. Their Area X-projecting HVC neurons fire locked to specific syllables and specific transitions. In repeated syllables, activity can be locked to onset, offset, or show syllable-locked, gradually-ramping spike rates. Still, the neural activity exhibits short-range history dependence, going one transition back (Fujimoto 2011).

Here we used projection neurons specific calcium indicators and head-mounted miniaturized microscopes to record from HVC of freely behaving canaries over a several week period. Canaries produce songs that are almost exclusively composed from multi-syllable phrases. The behavioral time scales range from tens of milliseconds (for the shortest syllables) to tens of seconds (for the longest phrases), and a complete song can last over a minute. Importantly, the syntax of canary songs is controlled separately from the syllables' identity (Gardner 2005) and exhibits long range structure of the order of phrases (Markowitz 2013).
We present early-stage data showing calcium events that are both syllable and phrase transition locked. The calcium indicator's slow decay time smooths the bursting activity of HVC projection neurons and the signal reflects the moving-average firing rate in phrases of rapid trills. But, many syllables are long enough to uncover individual syllable-locked bursts. We will report preliminary findings of single cell bursts locked to phrase order and syllable order within a phrase.
The finding that phrase transitions and syllables are distinct in canary HVC suggest that flexible motor behavior, as described in mammals, can be investigated in songbirds and that timing and sequencing of motor components may have separated neural correlates in the same brain region.

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Poster

067. Neural Control of Social Interactions: Sexual Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 067.01/HH7

Topic: F.02. Behavioral Neuroendocrinology

Title: Mating-induced c-fos in infralimbic prefrontal cortex is higher in sexually experienced than naive female rats

Authors: *S. H. MEERTS[1], M. R. ARNOLD, 55057[2], G. BIERLEIN-DE LA ROSA[2]
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Abstract: Female rats exhibit changes in paced mating behavior as a consequence of sexual experience; sexually experienced rats return to the male rat more quickly after intromissions, receive intromissions at a more rapid rate, and spend more time with the male rat as compared to sexually naïve rats during a test of paced mating behavior. The underlying changes in the brain responsible for the shift in paced mating behavior are unknown. Here we compared mating-induced c-fos immunoreactivity between sexually experienced and naïve female rats in brain regions sensitive to mating stimulation, the ventromedial nucleus of the hypothalamus (VMH) and the posterodorsal medial amygdala (MePD), and an area known to contribute to reward and be remodeled by sexual experience, the prefrontal cortex (PFC). Ovariectomized, female rats

were hormone-primed with 10 ug estradiol benzoate 48 h and 1 mg progesterone 4 h prior to either 6 paced mating encounters (experienced) or 6 control exposures to empty paced mating chambers (naïve). On the day of brain collection, both experienced and naïve rats mated to 10 intromissions under paced mating conditions and then underwent transcardial perfusion 60 min later. Significantly more c-fos was observed in the infralimbic (IL) subregion of the PFC in experienced relative to naïve rats, whereas c-fos expression in the VMH, MePD, cingulate, and prelimbic subregions of the PFC was comparable between groups. The greater IL activation suggests that mating may be more rewarding or less stressful to experienced female rats compared to rats mating for the first time. The PFC also participates in learning and suppression of impulsive behavior so additional research is needed to determine the role of the PFC in experience dependent shifts in paced mating behavior. Further research investigating other brain regions that modulate anxiety, such as the paraventricular nucleus, or reward, such as the nucleus accumbens, and the phenotype of the activated cells is also warranted.

Disclosures: S.H. Meerts: None. **M.R. Arnold:** None. **G. Bierlein-De La Rosa:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

Location: Halls A-C

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Program#/Poster#: 067.02/HH8

Topic: F.02. Behavioral Neuroendocrinology

Support: CONACYT 167773 GACA

CONACYT 353271 MBTS

CONACYT CVU 210442 DHC

CONACYT 429610 VXDE

Title: Cohabitation under enhanced D2-type activity with receptive females sensitizes olfactory-induced Fos-IR in intact, but not in early-gonadectomized male rats

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Abstract: Early-gonadectomized (EGx) males (PD1-PD3) do not express complete brain dimorphism and fail to display preference for receptive females (PD60). However, if those males are periodically allowed to cohabit with receptive females their interest increases (contact frequency, genital investigations, olfactory investigations, mount attempts, visits, time spent together). Interestingly, if cohabitation occurs under the effects of a D2-type receptor agonist (quinpirole) interest for females is intensified, although not to the level of gonadally-intact animals. Herein, we explored Fos-immunoreactivity (IR) in those males following exposure to female scent. Three groups of males were formed: Intact , EGx and Sham. On PD60 males were tested for unconditioned partner preference (UCPP) before one sexually receptive female and one stud male. Intact and Sham expressed an UCPP for the female. However, the EGx group failed to express any preference. Four days later each group cohabited with sexually-receptive females to induce conditioning, during 24 hrs every four days, for three trials. Half of each group received saline or quinpirole (1.25 mg/kg i.p.) before the start of cohabitation. Four days later they were tested for conditioned partner preference in a drug-free test. Experimental males that received quinpirole during conditioning expressed more olfactory and genital investigations, mount attempts, and time spent with the female partner. Only Intact and Sham displayed intromissions and ejaculations, but it was intensified by quinpirole. Four days later males were exposed during 60 min to woodshaving from boxes of sexually-receptive females. Brain were processed for Fos-IR in the following regions: N. accumbens shell (NAcSh), medial preoptic (mPOA), paraventricular nucleus of the hypothalamus (PVN), ventromedial nucleus (VMH), and medial amygdala (MeA). As compared to saline-treated males more Fos-IR was observed in the NAcSh of Intact-quinpirole and Sham-quinpirole males, but not in EGx-quinpirole. No differences were detected in other brain regions. These results suggest that cohabitation under enhanced D2-type activity with receptive females sensitizes the NAcSh of males with a functional gonad to the expression of Fos-IR upon exposure to female scent.

Disclosures: M. Barradas: None. **M.B. Tecamachaltzi-Silvarán:** None. **V.X. Díaz-Estrada:** None. **D. Herrera-Covarrubias:** None. **L.I. Garcia:** None. **P. Carrillo:** None. **J. Manzo:** None. **G.A. Coria-Avila:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 067.03/HH9

Topic: F.02. Behavioral Neuroendocrinology

Support: CNPq

CAPES

PROAP/UFCSPA

Title: Sexual experience induces spine-specific changes in pyramidal neurons of medial posterodorsal amygdala and CA2 hippocampal area of male mice

Authors: *M. GIOVENARDI, V. LAZZARI, R. BECKER, A. RASIA FILHO
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Abstract: The modulation of male sexual behavior involves contextual processing of sexual encounters and individual memories. In rodents, oxytocin (OT) binding activity in the medial posterodorsal nucleus of the amygdala (MePD) integrates the olfactory and pheromonal information and is involved in the regulation of social behaviors. Also, social memory processing is performed in the pyramidal neurons of hippocampal area CA2, which highly express OT receptors. OT is important to the modulation of neural circuits for social behaviors and the spine geometry can influence synaptic processing. Here, we describe the effects of sexual experience on density and shape of dendritic spines in the MePD and CA2 of male mice OT knockout. The males were allocated into four groups: wild-type naïve (WT/Naïve), OT knockout naïve (OTKO/Naïve), WT sexually experienced (WT/SexExp) and OTKO sexually experienced (OTKO/SexExp). For the sexual experience, each male was placed with two female mice along 3 weeks. The preparation of histological samples was made with Golgi method. The first 40 µm of MePD proximal dendrites and the first 10 µm of CA2 proximal dendrites had their spines drawn using a camera lucida coupled to an optic microscope. For each male, 2-8 different dendrites were studied with 1 dendrite per sampled neuron. The 3 main differently shaped spines (thin, mushroom, stubby/wide) were identified and counted from these samples. In the MePD, WT/SexExp and OTKO/SexExp group had significant decrease in density of dendritic spines of the tree forms studies (thin, mushroom and stubby/wide) when compared to WT/Naïve and OTKO/Naïve groups, respectively. Moreover, observed the OTKO/SexExp group had significant high in density of dendritic spines of the shape thin and mushroom in relation to WT/SexExp. Even plasticity in the CA2 seems to be tightly regulated, sexual experience was able to reduce the amount of stubby/wide spines, but did not affected density or other spines in CA2. Sexually experienced OTKO had a reduction of the number of stubby/wide smaller than WT animals. Perhaps the plasticity adaptation to sexual experience occurred better in WT animals than in OTKOs. Our results show that the spine-specific changes induced by sexual experience alter the normal synaptic processing and excitatory responses in the MePD and CA2, which can be important to regulate the social responses and to consolidate the memory of sexual experience.

Disclosures: M. Giovenardi: None. **V. Lazzari:** None. **R. Becker:** None. **A. Rasia Filho:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Support: NIH RO1 MH50388

Fonds Leon Fredericq ULg

non FRIA Grant ULg

FRS-FNRS

Title: Rapid changes in preoptic estradiol concentration during male sexual behavior

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Abstract: Estrogens such as estradiol (E_2) exert pleiotropic effects on physiological and behavioral responses such as neuroprotection, aggression or reproduction. Estrogens derived from local brain synthesis (neuroestrogens) are critical for the regulation of different functions including the control of male sexual behavior. Classically, E_2 acts through effects initiated in the nucleus to regulate male sexual function. Along with these long-term effects, E_2 also acts rapidly (within minutes) via membrane-initiated events. These effects are thought to depend on short-term variations in the local production of estrogens, through rapid fluctuations of the enzymatic activity of brain aromatase. In Japanese quail, rapid modulations of brain aromatase activity (AA) have been reported after sexual interactions or exposure to an acute stress. These changes take place mainly in the medial preoptic nucleus (POM), a sexually differentiated structure that plays a key role in the control of male sexual behavior and where aromatase is densely expressed. Yet, it has recently been shown that, in the short term, AA does not always reflect local E_2 concentration. This study was designed to determine by *in vivo* microdialysis whether local E_2 concentrations fluctuate during sexual interactions and test whether these changes parallel the decrease in AA observed ex vivo after copulation. We first conducted a series of experiments to validate the microdialysis and E_2 assay. When dialysis probes were placed in successive baths containing known increasing amounts of E_2, proportional changes in E_2 concentration were measured in the dialysate. Moreover, a rise in E_2 concentration was detected after in vivo retrodialysis of testosterone only if the probe was located within the POM and, after a peripheral injection of E_2, a sharp rise of E_2 was detected regardless of the probe location. Together these results show that in vivo microdialysis is a valid method to assess endogenous fluctuations of brain E_2 concentrations in behaving animals. Two independent experiments then identified a rise in E_2 concentrations in POM during sexual interactions. This increase occurred within 10 min after the initiation of the sexual interaction and was specific to the POM as there was no increase in E_2 concentrations in males that had their cannula outside of this area. Together these data confirm that rapid changes in AA measured ex vivo cannot be considered as a reliable proxy for E_2 concentrations. The discrepancies could originate either from the different

time resolution related to the two techniques or from differences in the microenvironment in which aromatase functions in vivo and during ex vivo assays.

Disclosures: M. de Bournonville: None. **C. De Bournonville:** None. **G.F. Ball:** None. **J. Balthazart:** None. **C.A. Cornil:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Program#/Poster#: 067.05/HH11

Topic: F.02. Behavioral Neuroendocrinology

Title: Preference for the same receptive female shown by a group of male rats in a multiple partner paradigm

Authors: *J. OLAYO-LORTIA, A. CRUZ-BENITES, A. MORALES-OTAL, A. FERREIRA-NUÑO
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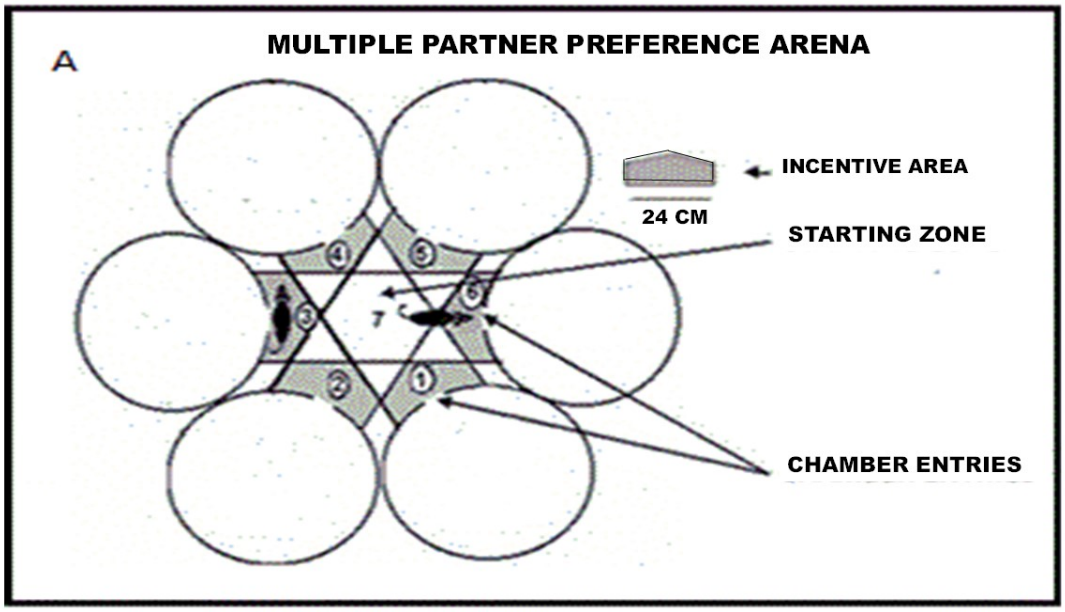
Abstract: In multiple partner paradigms (MPP), in which a male rat can choose from several females, it has been shown that male spend longer time and copulate more with the female visited in the first order. However, it is unknown if a group of male rats could choose the same female as a partner in this conditions. With this goal, a MPP made with 6 plexiglass cylinders placed in a closed circle was employed (Fig.A). In this MPP an experimental male (ExM) rat, introduced in the central compartment, could choose their partner between 4 receptive females (LQ < 90%) placed inside of the cylinders, through their respective access doors. The present experiment was repeated weekly 3 times identically with the same males (n=10) and females (n=4), that were numbered previously. Nevertheless, the criterion to end the initial trial was changed weekly. In the first week, once the ExM visited the first female, the initial trial was ended and the male was taken out. Then the females were moved to the next compartment following a clockwise direction and the same ExM was reintroduced in the MPP to score the female chosen in this trial. In the 2nd week the same experiment was done, but now the initial trial finished once the male made the first mount or intromission to the female of 1st entry. Finally, in the 3rd week, the initial test ended when the male ejaculated the female of 1st entry. In the three experiments, during the first trial, males did not prefer a particular female and their choice was random, while in the second trial, most males chose a different female from the one selected in the initial trial. However, interestingly in the 1st and 3rd weeks during the 2nd trial, 7 males out of 10 visited first the same female, regardless of the event that occurred in the initial trial (visit or ejaculation). Therefore, it is possible that a group of male rats would choose the same receptive female as a partner in a MPP. The possible reasons why the males were unable to

choose this female during the initial trial or in the experiment performed in the second week are discussed.



Disclosures: J. Olayo-Lortia: None. **A. Cruz-Benites:** None. **A. Morales-Otal:** None. **A. Ferreira-Nuño:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: UGRP Grant

Title: Effects of developmental aromatase inhibition, metabolism suppression, and endocrine disruption on parturition and early postnatal neuromuscular function in the Norway rat (Rattus norvegicus)

Authors: *G. M. LANGE, O. BISHOP, J. HACKER, M. WINDY, S. HOLIHAN
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Abstract: In classic work by William C. Young's laboratory, it was established that organization of mammalian brain morphology is guided by expressed gonadal hormones *in utero*. It has been

further established that specific enzymatic alteration of gonadal hormones can occur in the undifferentiated neuron. Therefore, the genetic sex of an organism drives phenotypic development of sexual morphology and the brain. Experiments involving manipulation of embryonic environments in *oviparous* avian and fish models has demonstrated phenotypic sex expression opposite that of genotype is possible. This phenotypic expression is possible both in body morphology and in brain organization. However, there are currently no *viviparous* organisms where induced phenotypic sex opposite of genotype has been demonstrated, most likely due to chemical complexities associated with internal gestation. Here, we report on effects of prenatal exposure to a chemical cocktail, specifically use of tamoxifen, thiouracil, and corticosterone at environmentally relevant levels that may influence early development by reshaping the mammalian intrauterine environment enough to permit phenotypic expression of sexual morphology opposite that of genotype in mammals. We present a detailed look at our experimental design n the Norway rat. In this research model, sexually indifferent morphology is maintained through gestational day 10 following fertilization. Our chemical mixture has been introduced to our subjects beginning within this undifferentiated developmental stage of sexual organization and continued through parturition. Parturition difficulties were observed in our dams exposed to this chemical cocktail. Administration of this chemical mixture to the intrauterine environment appears to have impacted gestation in ways that have altered development resulting in changes in morphology of the anogenital region and impacted righting responses as well as other functional measures of growth. In future work, we plan to establish pup performance on a variety of post-natal behavioral and morphological tests relevant to sex differentiation, including brain organization, especially of the sexually dimorphic nucleus. By comparing control and treatment populations at the neural, morphological, reproductive, and behavioral levels, we hope to gain deeper insight into the mechanisms driving sexual differentiation in mammals.

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Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Support: Technical support Camacho F.

CONACYT 253631

Fronteras 374

DGAPA-UNAM IN210215

Title: The expression of mu opioid receptor 1 (OPRm1) in different brain areas of male rats varies depending on the time of sacrifice after they copulated

Authors: M. BEDOS, A. ANTARAMIAN, A. GONZALEZ-GALLARDO, *R. G. PAREDES
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Abstract: Mating induces a positive affective state which is blocked by the systemic administration of naloxone, a specific opioid antagonist. Opioids are released in the medial preoptic area (mPOA) and other brain regions during sexual behavior and mu opioids receptors are activated in males that copulate until ejaculation. The aim of the present study was to determine if mating increases the expression of OPRm1 in areas involved in the control of sexual behavior, namely the mPOA, the ventromedial hypothalamus (VMH) and the amygdala (AMY) in male rats. We used ninety sexually experienced Wistar male rats that were randomly assigned to the following groups (n=10 each) : a) Paced (P), males were allowed to mate, pacing the sexual interaction; b) Non Paced (NP), males were allowed to mate without pacing the sexual interaction; c) Control (C), males were able to hear, see and smell a sexually receptive female, but no physical contact was possible. Sexual behavior tests lasted 1h and the following parameters were recorded: number of mounts and intromissions (NM and NI), latency to the first mount, intromission and ejaculation (ML,IL and EL), and the postejaculatory interval (time from ejaculation until the next intromission). Males were sacrificed by decapitation 4, 8 or 12 h after the behavioral tests (n=10 each). The mPOA, VMH, AMY and the cortex (CTX) as control were dissected. After RNA isolation and cDNA synthesis, expression of the OPRm1 mRNA was determined by qPCR in duplicates. No significant differences were found among P, NP and C groups in the expression of OPRm1 in the mPOA and the AMY independently of the time. In the VMH, the expression of OPRm1 increased in the P compared to the C group at 4h. No significant differences were found in this area at 8 and 12h. In the CTX, expression of the receptor was not detectable. Interestingly, we found that the expression of OPRm1 varied at the different times of sacrifice. In the mPOA, its expression increased between 4 and 8h and then decreased from 8 to 12h, independently of the experimental group. In the VMH, OPRm1 expression decreased when comparing 4h and 12h, independently of the experimental group. In the AMY, we found an increase of OPRm1 expression between 4 and 8 h in the C and NP groups. No effect of the time was detected in this area in the P group. In conclusion, our results show that the expression of OPRm1 in different brain areas varied depending on the time of sacrifice after mating.

Disclosures: M. Bedos: None. **A. Antaramian:** None. **A. Gonzalez-Gallardo:** None. **R.G. Paredes:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Program#/Poster#: 067.08/HH14

Topic: F.02. Behavioral Neuroendocrinology

Title: Exploring the rewarding effect of sexual contacts in the partner preference of the rat

Authors: *A. MORALES-OTAL[1], J. OLAYO-LORTIA[2], A. CRUZ-BENITES[3], A. FERREIRA-NUÑO[3]
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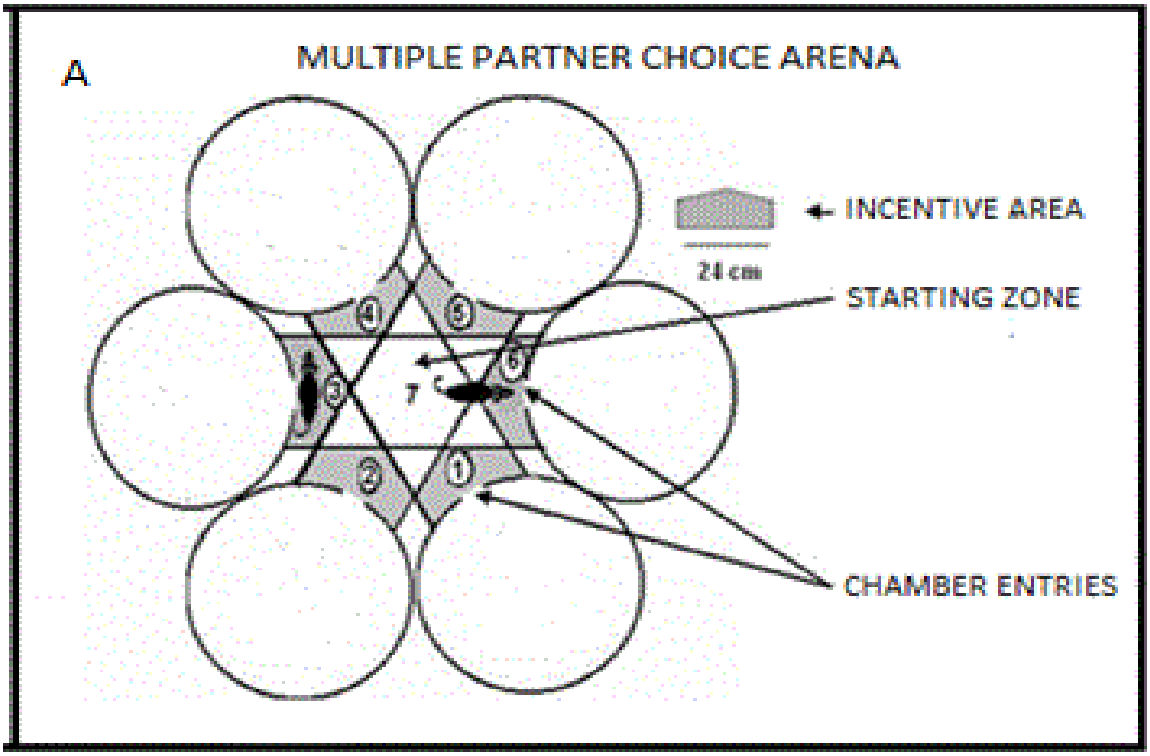
Abstract: In the rat, it has been shown that males spend longer time and copulate more with the female visited in the first order, when is tested in a multiple partner paradigms (MPP). It has been proposed that the rewarding effect the female induces in the male, through the sexual contacts, is responsible for this behavior. To verify this hypothesis, a MPP made with 6 plexiglass cylinders, placed in a closed circle was employed (Fig.A). An experimental male (ExM) rat introduced in the central compartment was allowed to choose their partner between 4 receptive females (LQ < 90%) placed inside of cylinders, through their respective access doors. This first experiment was repeated during 3 weeks with the same group of males (n=10) and the same 4 stimuli females, previously numbered, changing the conditions each week. In the first week, once the ExM visited the first female, the initial test was ended and the male was taken out. Then the females were moved to the next compartment following a clockwise direction and the same ExM was reintroduced in the MPP, to observe if he chooses the same female, based on the experience obtained during the previous test. In the 2nd week the same experiment was done, but now initial test finished once the male made the first mount or intromission to the female of 1st entry. Finally in the 3rd week, the initial test ended when the male ejaculated the female of 1st entry. In a second experiment we do the same but the order of the sexes was reversed. In this case 7 sexually receptive female was allowed to choose among 4 sexually expert males, previously numbered. During the experiments, the stimuli subjects were ever the same. In both studies during the second trial, the experimental subject was incapable to select the same partner chosen in the initial test, based on the experience obtained previously. Therefore, the rewarding effect that the experimental subject obtains from sexual interactions with their first partner chosen is not enough to maintain this preference.



Disclosures: **A. Morales-Otal:** None. **J. Olayo-Lortia:** None. **A. Cruz-Benites:** None. **A. Ferreira-Nuño:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Title: Effects of a bee mixture on sexual behavior and testosterone levels in rabbits

Authors: ***J. L. MENDOZA-ESCALONA**[1], P. VERGARA-ARAGON[3], M. PIZARRO-RODAS[4], B. I. MEZA AUPART[2], T. NERI-GOMEZ[5], R. B. GARCIA[6]
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Abstract: In preliminary studies it has been observed that the daily consumption of apicultural products in the conventional diet of orchiectomized rats produces a neuroprotective and

gonadoprotector effect. The purpose of this study was to determine the effects of daily intake of a bee mixture on body weight, feed intake, sexual behavior and testosterone levels in orchiectomized rabbits. Twenty-four white New Zealand rabbits (males) of four months old were employed. The animals were randomly divided into 4 groups: 1) control group (no treatment); 2) rabbits without surgery (Qx) and that received the bee mixture (MA); 3) with surgery and without bee mixture; 4) with surgery and bee mixture. Animals received treatment for 42 days (1.0 g / day / each 5kg PV / v.o.). Food intake was determined daily, rabbit weight was reported each week, in addition to a video-record for the analysis of sexual behavior and testosterone levels were determined. The results indicated that the group with surgery (Qx) without bee mixture (MA) showed a significant increase in body weight with respect to the group with Qx + MA, while the group without Qx with MA showed no difference with the control. The food intake registration did not report differences between groups. On the other hand, the group without Qx + MA increased the sexual response to the female, showing significant differences with respect to the Qx without MA. Testosterone levels indicated a significant increase in the group without Qx + MA with the rest of the experimental groups. The results suggest that MA does not increase body weight or alterations in food intake, improve the sexual response of orchiectomized rabbits and increases testosterone levels in uncastrated rabbits. Frequent food intake of bee products in the conventional diet of healthy rabbits is likely to have a beneficial effect by increasing reproduction for prolonged periods of time and maintaining normal testosterone levels.

Disclosures: J.L. Mendoza-Escalona: None. **P. Vergara-Aragon:** None. **M. Pizarro-Rodas:** None. **B.I. Meza Aupart:** None. **T. Neri-Gomez:** None. **R.B. Garcia:** None.

Poster

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant R03AG049255

NIH Grant R01NS088514

Title: Chronic intermittent hypoxia advances hormonal aging and induces sexual dysfunction in male rats: Implications for parkinson’s related non-motor symptoms

Authors: *R. L. CUNNINGHAM[1], D. A. SCHRIEHOFER[2], M. ANDERSON[2]
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Abstract: Sleep apnea is a common comorbidity of Parkinson's disease (PD) and is itself a risk factor for the development of PD, particularly in men. Also in men, both sleep apnea and PD are associated with sexual dysfunction. Despite having a significant negative impact on quality of life, non-motor symptoms of PD such as sexual dysfunction are relatively understudied, in part due to the lack of a suitable animal model. Chronic intermittent hypoxia (CIH) is a model that encompasses elements of both sleep apnea and PD. Specifically, CIH replicates the repetitive hypoxic conditions that characterize sleep apnea, and at the same time CIH induces oxidative stress (OS) and neuroinflammation in brain regions that are damaged/destroyed in PD. However, it is unknown whether CIH causes sexual dysfunction in males. Therefore, we examined the role of CIH on sex behaviors, steroid hormones, neuropeptides associated with social behaviors, and OS generation in young (3-months) and old (12-months) male F344/BNF1 rats. The CIH model consisted of placing caged rats in a sealed chamber that allowed for the exchange of atmospheric gases. Over a period of 10 days divided into 8 hour daily sessions, oxygen levels were cycled between 21% to 10% over a span six minutes before returning to normal oxygen levels. Sex behavioral testing was carried out on day nine and assessed the frequency and latencies of mounts, intromissions, and ejaculations. Blood plasma samples were obtained on day ten and were used to measure testosterone (T), corticosterone (C), vasopressin (AVP), oxytocin (OXY), and advanced oxidation protein products (AOPP). In normoxic (control) conditions, old rats had impaired sexual behaviors compared to young rats, as indicated by significantly reduced mount and intromission frequencies and increased latency times. CIH, however, induced sexual dysfunction in young rats with results comparable to those seen in old rats. Accordingly, in young rats CIH decreased T, increased C, and increased OS, as indicated by AOPP. CIH did not alter OXY and AVP in young rats. Interestingly, in old rats CIH had no effect on sexual behavior, T, C, OXY, or AVP, indicating that age may have a ceiling effect. These results show that CIH induces male sexual dysfunction, advances hormonal aging, and increases markers of oxidative stress. This suggest that sleep apnea may exacerbate non-motor symptoms of PD and contribute to decreased quality of life in PD patients. Further studies using the CIH model for may offer insight into the mechanisms underlying these effects and the possible feedback loop between sleep apnea and PD.

Disclosures: R.L. Cunningham: None. **D.A. Schriehofer:** None. **M. Anderson:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: Norwegian Research Council grant 251320

Title: Involvement of glutamatergic medial amygdala neurons in ejaculation in male rats

Authors: *P. T. HUIJGENS, R. HEIJKOOP, E. M. S. SNOEREN
Dept. of Psychology, UiT The Arctic Univ. of Norway, Tromso, Norway

Abstract: Lesion studies have shown that the medial amygdala (MeA) is involved in sexual behavior in male rats. Limitations of these studies include the lack of distinction between neuronal cell types, effects on passing projections, and inability to target specific projections. Here, we investigated the role of glutamatergic MeA neurons, and their specific projections to the preoptic area (POA), a brain area that is also well-known to be involved in sexual behavior. AAV5-CaMKIIa viral vector constructs coding for GFP (control), stimulatory (hM3D), or inhibitory (hM4D) DREADDs were bilaterally injected into the MeA and a bilateral guide cannula was placed above the POA. Rats (n = 18-20 per group) were assessed in the sexual incentive motivation test and the copulation test upon systemic administration of the DREADD ligand, clozapine-N-oxide (CNO), silencing or stimulating glutamatergic neurons originating from the MeA. The same tests were conducted after intracranial infusion of CNO into the POA, which enables exclusive observation of effects of the direct, glutamatergic MeA-POA projections when stimulated or silenced.
The data show a decreased number of ejaculations and an increased ejaculation latency in the copulation test upon systemic administration of CNO as compared to both vehicle and the control group, an effect found in both experimental groups (stimulatory and inhibitory). In contrast, no effect was observed on sexual motivation or copulatory behaviors. Based on preliminary results, silencing or stimulating the specific MeA-POA glutamatergic projection did not affect sexual motivation and behavior.
Our study indicates that MeA glutamatergic projections are involved in ejaculation, but not in other copulatory phases. These effects do not seem to be regulated by direct, glutamatergic MeA-POA projections. The convergence of the behavioral effects of stimulating as well as silencing glutamatergic MeA projections may reflect effects through different indirect pathways. Future research should focus on unraveling these pathways.

Disclosures: P.T. Huijgens: None. **R. Heijkoop:** None. **E.M.S. Snoeren:** None.

Poster

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Support: NSF IOS 1256799

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NIH T32 GM008471

University of Minnesota Doctoral Dissertation Research Fellowship

Title: Investigation of glutamatergic circuitry underlying copulatory reward of sexual behavior in female Syrian hamsters

Authors: *K. M. MOORE, R. L. MEISEL
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Abstract: The nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) are brain regions known for their integral role in the processing of reward and motivated behaviors. Our lab utilizes sexual behavior in female hamsters to examine the underlying circuitry and mechanisms of naturally-rewarding behavior. Previous work in our lab has demonstrated increased dopamine release in the NAc during sexual behavior, and that this dopaminergic neurotransmission is necessary for sexual reward to occur. Recently, we have also shown that a similar pattern of glutamate release takes place in the NAc during sexual behavior. The aim of the present study is to investigate the underlying circuity of this sex-induced glutamatergic neurotransmission. We first evaluated potential sex-activated afferents to the NAc from the mPFC using stereotaxic injections of the monosynaptic retrograde tracer Choleratoxin subunit B (CTB) into the core of the NAc and subsequent immunohistochemical staining for cFos, a marker of neuronal activity. We confirmed our lab's previous findings that sexual behavior increases cFos expression in the NAc core, and to a lesser but still significant extent, the shell. Further, we showed that there was increased c-Fos staining in the mPFC, including both infralimbic and prelimbic regions, though the increase in c-Fos staining localized to CTB neurons showed only a trend towards significance. To further dissect this circuit, we utilized immunohistochemical indicators of GABA or glutamate cells in the mPFC, along with cFos, to elucidate which population of mPFC cells were activated by sexual behavior. Utilizing a different approach, we also performed stereotaxic injections of an AAV expressing an inhibitory DREADD with a CaMKII promotor (to target glutamatergic neurons) in the mPFC. Here our goal is to silence mPFC glutamatergic neurons to determine whether the activation of the NAc by female sex behavior is driven by the mPFC. Collectively, these studies elucidate for the first time components of the mesolimbic-cortical circuits mediating the rewarding consequences of female sexual behavior.

Disclosures: K.M. Moore: None. **R.L. Meisel:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 067.13/HH19

Topic: F.02. Behavioral Neuroendocrinology

Support: CONACYT CVU 210442 DHC

CONACYT 429610 VXDE

Title: Effect of acute LPS treatment on juvenile play behavior and adult sexual behavior

Authors: Y. Z. LEÓN-AHUMADA[1], V. X. DÍAZ-ESTRADA[1], M. BARRADAS[2], *D. HERRERA-COVARRUBIAS[3], P. CARRILLO[4], L. I. GARCIA[2], J. MANZO[5], G. A. CORIA-AVILA[6]
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Abstract: Puberty is a critical period for development in which individuals experience drastic neuroendocrine changes due to the transition from a non-reproductive towards a reproductive age. Exposure to stress during puberty may result in long-term behavioral alterations. For example, female mice, display lower levels of sexual receptivity in adulthood when exposed to an immune challenge (LPS treatment) during puberty. The present study investigated the effects of LPS during puberty on the play behavior of juvenile male rats, and also on their sexual partner preference in adulthood. Thus, play and social behavior (dorsal contacts, rough & tumble, boxing, olfactory and genital investigations) were scored daily for 10 min in pairs of Wistar males from PD33-PD42. On PD37 males received an intraperitoneal injection of 1 ml/kg of saline (control group) or 1.5 mg/kg of E. coli lipopolysaccharide (LPS group). Sickness behaviors (ptosis, huddling, piloerection, lethargy, xiphosis) were scored 1, 2, 4, 8, 24, 48 h after the injections. LPS induced sickness during the first 8 h only. Interestingly, play behavior decreased by age, but not by treatment, and genital investigations increased by age. On PD60, PD64, PD68 males were tested for sexual partner preference in a T-shaped chamber that contained a sexually-receptive female and a stud male as partners at the same time. In general, sexual preference was directed towards the female in both groups (Control and LPS). No significant differences were detected in the sexual performance between controls and LPS males. These data indicate that pubertal treatment with LPS do not affect juvenile play or adult sexual behaviors in male rats.

Disclosures: Y.Z. León-Ahumada: None. **V.X. Díaz-Estrada:** None. **M. Barradas:** None. **D. Herrera-Covarrubias:** None. **P. Carrillo:** None. **L.I. Garcia:** None. **J. Manzo:** None. **G.A. Coria-Avila:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: F32HD071755

NS034950

MH101373

IOS-0923588

DK090065

MH099647

Title: Identifying neural bases of social behavior with CRISPR/Cas9 and transgenesis in the cichlid Astatotilapia burtoni

Authors: *S. A. JUNTTI[1,2], P. MOURRAIN[3], R. D. FERNALD[2]
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Abstract: Across the animal kingdom, hormones serve to coordinate the physiology of diverse tissues. In the brain, these signals exert powerful influences on behavior. Therefore, hormonal control of fascinating behavioral displays exhibited in numerous species offers a tantalizing entry point to understand brain function. However, for the majority of species, it has been difficult to gain a mechanistic understanding of the cellular processes at work due to technical constraints. Recently, CRISPR/Cas9 has emerged as a potent tool for manipulating the genome of any species desired, in principle. The cichlid fish family displays a wide range of social behaviors that are regulated by hormonal signals. I describe the use of CRISPR gene editing in the cichlid *Astatotilapia burtoni* to manipulate prostaglandin F (PGF) signaling. Combining molecular genetics with behavioral analysis and other tools, we dissect the molecular genetic control of social behavior in *A. burtoni* to show that PGF signaling is necessary and sufficient for female sexual behavior. Our work also shows that the cells sensitive to PGF are central nodes in the female behavior circuit that is responsive to a variety of hormones. CRISPR and high-throughput sequencing also now permit the genetic study of phenotypes exhibited across cichlid species, including mate choice, parenting, monogamy, and social hierarchies.

Disclosures: S.A. Juntti: None. **P. Mourrain:** None. **R.D. Fernald:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant 8UL1GM118979-02

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Title: Dopamine receptor D1 is in close proximity with progesterone receptor and Src kinase complex to mediate progesterone signaling in the arcuate nucleus of the hypothalamus

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[1]Biol. Sci., California State Univ. Long Beach, Long Beach, CA; [2]Biol. Sci., California State University, Long Beach, Long Beach, CA

Abstract: Progesterone facilitation of sexual receptivity (lordosis) requires classical progesterone receptors (PGR), which are upregulated in the arcuate nucleus of the hypothalamus (ARH) by estradiol priming. Progesterone infusion into the ARH of ovariectomized (OVX) rats primed with 2 µg of estradiol benzoate (EB) facilitates lordosis within 30 minutes. This rapid action of progesterone is mediated by extranuclear PGR (PGR-B) that appear to directly inhibit ARH β-endorphin (β-END) neuronal transmission to induce lordosis. The rapid facilitation of lordosis by progesterone is mediated through PGR-B that complex with and signal through Src family kinase (Src). PGR-Src signaling that facilitates lordosis is interdependent with the dopamine receptor (D1/D5) signaling. Blocking either PGR, Src, or D1 activity blocks the ability of the other two to facilitate lordosis. We have demonstrated by immunohistochemistry that ARH β-END neurons express PGR, Src, and D1. Co-immunoprecipitation experiments revealed that PGR-B and Src form complex in membrane fractions of the ARH. However, the D1/D5 receptor did not appear to be physically complexed to either PGR or Src. Thus, we tested the hypothesis that a subpopulation of ARH neurons have D1 in close proximity to the PGR-Src complex. The Duolink In Situ Fluorescence (Sigma Aldrich) technique was used to demonstrate the close proximity of D1 to Src. This technique labels two proteins in close proximity via linking two host specific antibodies, and was counterstained with DAPI. Free floating sections taken through ARH from OVX Long Evans rats treated with EB (2 µg) that were fixed by transcardial perfusion of chilled saline followed by 4% paraformaldehyde 30 hours after EB. First, we probed for PGR and Src (Cell Signaling) as positive control for Duolink staining. We then tested whether D1 and Src are in close proximity. Duolink In Situ analysis showed that D1 is in close proximity to Src as indicated by speckled immunopositive staining located on the membrane of a subpopulation of ARH neurons. Our results suggest that D1 may not be complexed to PGR-Src, but is in close proximity to Src, which would allow for the interdependence of PGR, Src, and D1 signaling in the ARH that facilitates lordosis.

Disclosures: **M. Feri:** None. **R. Tominna:** None. **K. Sinchak:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: RO1HD058638

NSF Grant HRD-1302873

Title: Subsets of arcuate nucleus β-endorphin neurons co-express progesterone receptor, dopamine receptor D1, and Src family kinase

Authors: *M. ESKANDER, N. KHAN, J. RAZON, T. CHUON, K. SINCHAK
Biol. Sci., California State Univ. Long Beach, Long Beach, CA

Abstract: In ovariectomized (OVX) rats, β-endorphin (β-END) neurons in the arcuate nucleus of the hypothalamus (ARH) that project to the medial preoptic nucleus (MPN) are indirectly activated by priming with estradiol benzoate (EB, 2μg). This activation of β-END neurons inhibits sexual receptivity (lordosis). Simultaneously, EB priming upregulates classical progesterone receptor (PGR) expression in ARH β-END neurons. A subsequent dose of progesterone facilitates sexual receptivity within 30 minutes by inhibiting β-END neurotransmission in the MPN. Our previous findings indicate progesterone acts through PGR trafficked to the membrane that complex with and signal through Src family kinase (Src). This PGR-Src signaling in β-END neurons is interdependent with dopamine receptor (D1/D5) signaling: antagonizing one blocks facilitation of sexual receptivity by the other two. Previously, using double-label immunohistochemistry we demonstrated that subpopulations of ARH β-END neurons co-express PGR, D1 and Src. In this experiment, we used triple-label immunohistochemistry to demonstrate that subsets of ARH β-END neurons express combinations of PGR, Src, and D1. We triple-labeled for PGR/Src/D1, β-END/Src/PGR, and β-END/D1/PGR in EB primed and oil treated OVX rats. For each of the three combinations, we observed subpopulations of immunopositive cells with PGR/Src/D1, β-END/Src/PGR, and β-END/D1/PGR in both treatment groups. However, our preliminary data indicate that estradiol treatment increases co-expression. The percentage of β-END neurons that express Src/PGR (β-END/Src/PGR) increased from 1.9% (oil) to 18.9% after EB treatment. Similarly, the percentage of β-END neurons immunopositive for D1/PGR (β-END/D1/PGR) increased from 1.6% (oil) to 28.9% after EB treatment. Thus, our data indicate that EB increases the coexpression of PGR/Src/D1 in ARH β-END. These results provide anatomical support for interdependent signaling of PGR-Src-D1 within subpopulations of ARH β-END neurons to facilitate lordosis.

Disclosures: **M. Eskander:** None. **N. Khan:** None. **J. Razon:** None. **T. Chuon:** None. **K. Sinchak:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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RISE Grant GM07163

Howell Grant 8RL5GM118979-02

Title: Membrane impermeable estradiol (E-Biotin) rapidly facilitates lordosis through G protein-coupled estrogen receptor-1 (GPER)

Authors: *S. M. CHOKR, R. TOMINNA, K. SINCHAK
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Abstract: In a 2µg estradiol benzoate (EB) primed ovariectomized (OVX) rat, sexual receptivity (lordosis) can be facilitated via sequential activation of estrogen receptor-α (ERα) and G protein-coupled estrogen receptor-1 (GPER; aka GPR30) in the arcuate nucleus of the hypothalamus (ARH). EB priming indirectly activates β-endorphin (β-END) neurons through a multisynaptic neurocircuit in the ARH that projects to the medial preoptic nucleus (MPN) to activate µ-opioid receptors (MOP), which inhibits lordosis. Infusion of non-esterified 17β-estradiol benzoate (E2) into the ARH 47.5 hours after EB priming facilitates lordosis within 30 minutes. The rapid actions of E2 are mediated by GPER that activates the orphanin FQ-orphanin receptor-like receptor-1 (OFQ/N-ORL-1) system to rapidly reduce MPN MOP via inhibition of β-END neurons to facilitate lordosis. Our previous studies showed that GPER is present in 85.7% of ARH OFQ/N neurons (Tran et al 2015). Using cell fractionation techniques and western blot we demonstrated that GPER are expressed both in plasma membrane and cytosolic ARH fractions (Feri et al 2016). Therefore, we tested the hypothesis that GPER on the plasma membrane mediate the rapid OFQ/N-ORL-1 signaling pathway to deactivate MPN MOP and facilitate lordosis. OVX Long Evans rats implanted with bilateral cannulae aimed at the ARH were EB-primed and received ARH infusion of E2 or 17β-estradiol-biotin (E-Biotin) 47.5 hours after EB-priming. Both treatments facilitated sexual receptivity (measured by lordosis quotient; LQ) within 30 minutes. Rats pretreated with G15, GPER antagonist, or UFP-101, ORL-1 selective antagonist, prior to E-Biotin had significantly lower LQ's compared to the saline pretreated

group. These data indicate that the rapid GPER signaling that facilitates lordosis is initiated at the level of the plasma membrane and signals through the OFQ/N-ORL-1 system. It is apparent that multiple ER pathways are activated over time to regulate sexual behavior. Knowing when and which ER signaling pathway is mediating estrogenic signaling is important for understanding estrogenic actions and better directing estrogen therapies.

Disclosures: S.M. Chokr: None. **R. Tominna:** None. **K. Sinchak:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIDA R01 DA013185

NICHD T32 HD007228

Title: Arcuate nucleus-specific chemogenetic activation of the lordosis-regulating circuit

Authors: *L. M. RUDOLPH, T. M. CARDINAL, P. E. MICEVYCH
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Abstract: In female rodents, lordosis is an indication of sexual receptivity. An important part of the hypothalamic circuit controlling lordosis involves two distinct neuronal populations within the arcuate nucleus of the hypothalamus (ARH): neuropeptide Y (NPY) and proopiomelanocortin (POMC) neurons. Previous experiments suggest that estradiol acts through membrane estrogen receptors (mERs) to stimulate the NPY release and activate POMC neurons, which project to the medial preoptic nucleus (MPN). Activation of this circuit transiently inhibits lordosis behavior. To begin a functional analysis of this circuit, we chemogenetically activated each defined arcuate neuronal population involved in the circuit (e.g., POMC and NPY) using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). DREADDs were expressed in the ARH of POMC-cre and Agrp-Ires-cre (NPY) neurons of adult female mice (breeding pairs obtained from Jackson Laboratories) and subsequently activated with the specific ligand, clozapine N-oxide (CNO; TOCRIS). Briefly, Cre-dependent AAVs coding for Gq-coupled DREADDs (rAAV5/hsvn-DIO-hm3D-mcherry, 200 nL/side, UNC Vector Core) were delivered bilaterally to the ARH (mm from bregma: A/P = - 1.4; M/L = ± 0.4; D/V = - 5.5) of adult female mice using standard aseptic stereotaxic surgical techniques. Animals were ovariectomized (ovx) and allowed to recover before further treatment. Three weeks after AAV delivery mice were steroid primed prior to behavioral testing. Ovx females received 2 injections of 10 μg of EB at 48 and 24 h before testing. On the morning of testing, mice received 500 μg of

progesterone. An experienced male was placed into a testing arena and allowed to habituate before females was placed individually with the male for 10 min, or until 10 vigorous mounts occurred. Sexual receptivity was quantified by calculating a lordosis quotient. After the first round of behavioral testing, sexually receptive females received CNO (30 mg/kg, i.p.), the Gq-DREADD agonist. 15-30 min after CNO injection, sexually receptive females were included in a second round of behavioral testing. After behavioral testing, animals were euthanized and transcardially perfused. Brains were removed and sectioned to confirm DREADDs expression in the ARH and MPN. Preliminary data demonstrate that activation of POMC neurons with CNO decreased lordosis behavior in sexually receptive female mice. These results with POMC neurons activation confirm earlier knockout studies that showed that μ-opioid receptor activation regulates lordosis.

Disclosures: **L.M. Rudolph:** None. **T.M. Cardinal:** None. **P.E. Micevych:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

Location: Halls A-C

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Topic: F.02. Behavioral Neuroendocrinology

Support: CONACYT grant 420383

CONACYT grant 217854

Title: Comparision of female´s sexual behavior in the paced and non-paced mating paradigms using two different rat models of diabetes

Authors: *A. K. HERNÁNDEZ, D. REBOLLEDO SOLLERIO, A. FERNÁNDEZ-GUASTI
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Abstract: The relationship between diabetes mellitus (DM) and sexual dysfunction in women has not been fully established, and has yielded controversial results. Almost all preclinical reports that study this association utilize a model of diabetes mellitus 1 (DM1) by administering streptozotocin (STZ) to young-adult rats, whereas there is only one study using a model of type 2 diabetes mellitus (DM2) that injected STZ in the neonatal stage. All these reports have used the non-paced mating (NPM) to evaluate female sexual behavior (FSB). Paced mating (PM) is a condition where females control the rate of sexual stimulation they received; under such condition, FSB has not been analyzed in diabetic rats. Thus, the aim of this study was to evaluate FSB -in NPM and PM- using two different models of DM. For DM1, ovariectomized (OVX) Wistar rats, 11 weeks old, were injected with STZ (50 mg/kg, i.p., for 2 consecutive days). Body weight (BW) was recorded at the beginning and at the end of the study; 10 days after STZ

injections, behavioral tests were performed in animals with glucose values ≥ 350 mg/dl. DM2 was induced in female Wistar pups of 3-4 days by injecting STZ (70 mg/kg, i.p.). BW gain was recorded weekly until the end of the experiment. An oral glucose tolerance test was performed at the 8th week of age, administering a sucrose solution (2 g/kg); animals were included if glucose levels were ≥250 mg/dl after the sucrose insult. Controls were i.p. injected with citrate buffer vehicle. Behavioral tests were conducted in OVX rats when they were 12 weeks old. Rats received estradiol (10 µg, -24 h) + progesterone (3 mg, -4h) to induce sexual receptivity. In both copulating conditions, NPM and PM, we registered the lordosis quotient (LQ) and intensity of lordosis (IL) in response to male mounts or intromissions, as well as the number of proceptive and aggressive behaviors (AB). In the PM we also calculated the % of female's exits from the male's chamber following stimulation and the return latencies. Rats modeling DM1 showed BW loss when compared to controls, whereas the BW did not change in rats with DM2. In NPM, hyperglycemic animals (both, DM1 and DM2) showed a reduction in LQ and IL and an increase in AB, without changes in proceptivity. However, in PM, the reduction in LQ and IL in DM1 rats was not observed in DM2 females. No changes in proceptivity or AB were found in diabetic animals (DM1 or DM2) using PM. Our data suggest that the reduced FSB relates to the intensity of hyperglycemia and not to the ability of the female to control mating.
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Disclosures: A.K. Hernández: None. **D. Rebolledo Sollerio:** None. **A. Fernández-Guasti:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: CONACYT 611071 RRR

CONACYT 429610 VXDE

CONACYT CVU 210442 DHC

Title: Conditioned sexual arousal towards infants in adult male rats: A model of learned pedophilia?

Authors: R. RAMIREZ-RODRIGUEZ[1], D. PERUSQUÍA-CABRERA[2], V. X. DÍAZ-ESTRADA[1], D. HERRERA-COVARRUBIAS[3], P. CARRILLO[1], L. I. GARCIA[3], J. MANZO[4], *G. A. CORIA-AVILA[5]
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Abstract: Sexual preferences can be strengthened, weakened or drastically modified via conditioning, specially during certain neurochemical states. For example, cohabitation with another individual under the effects of Quinpirole (a D2-type receptor agonist) induces a conditioned socio-sexual partner preference. Such preference is powerful enough to be directed towards same-sex individuals and occurs in sexually naïve males, but not in studs. In those studies naïve rats are allowed to cohabit during 24 h every four days, for three trials with a sexually experienced male rat that bears almond odor on the back as a conditioned stimulus. During a drug-free final test, males choose between the familiar scented male rat or a novel sexually receptive female. Conditioned males display sexual and social preference for the scented male over the sexually receptive female. They spend more time with the male, display body contacts and more non-contact erections. Herein, we explored the effects of this type of conditioning on the development of conditioned preference for infants. Thus, 20 adult males sexually-naïve were organized into two groups (conditioned and control). Conditioning consisted of cohabitation for 24 h with an infant male (25 day old) that bore almond scent as conditioned stimulus. Prior to each conditioning trial the conditioned group received quinpirole (1.25 mg/kg, i.p.) whereas control males received saline. This was repeated every four days for a total of three trials. Four days after the last conditioning trial rats were tested for partner preference in a T-shaped chamber. In one goal compartment there was the young almond scented infant (now 41 days old) and in the other compartment a sexually-receptive adult female rat. We assessed social and sexual behaviors during 20 min. In addition, rats were tested for non-contact erections during exposure to either infants or females. Results failed to show any social or sexual preference for either partner in both groups. Interestingly, the test for non-contact erections indicated a significant effect of conditioning. Control males displayed more erections during exposure to a sexually-receptive female, whereas conditioned males displayed more erections during exposure to the infant. Our results suggest that conditioned males experienced more sexual arousal towards scented infants (conditioned stimulus) than towards sexually receptive female (unconditioned stimulus). Accordingly, cohabitation with novel infants under the effects of D2-type agonists may explain some cases of learned sexual arousal towards sexually-inmature individuals. We suggest this as a model of learned pedophilia.

Disclosures: R. Ramirez-Rodriguez: None. **D. Perusquía-Cabrera:** None. **V.X. Díaz-Estrada:** None. **D. Herrera-Covarrubias:** None. **P. Carrillo:** None. **L.I. Garcia:** None. **J. Manzo:** None. **G.A. Coria-Avila:** None.

Poster

067. Neural Control of Social Interactions: Sexual Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: F.02. Behavioral Neuroendocrinology

Support: Natural Sciences and Engineering Research Council of Canada (NSERC)

Title: Cortisol, DHEA-S and eyeblink as measures of shock-induced anxiety during neutral and sexual stimuli

Authors: *L. D. HAMILTON, K. R. PETERS, A. M. RUSSELL
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Abstract: Anxiety has been repeatedly shown to have an influence on sexual arousal, but the direction of this effect has been mixed. Some studies have found facilitatory effects, while others have found inhibitory effects. The goal of the present studies was to examine mechanisms that might explain the differing results. In particular, we were interested in the role of salivary cortisol and dehydroepiandrosterone-sulfate (DHEAS) in moderating this relationship. Study 1 tested a modified version the Neutral-Predictable-Unpredictable (NPU) threat protocol (Schmitz & Grillon, 2012) adapted to be used with film stimuli during the test phase. Participants (N = 60) were trained in neutral, predictable, and unpredictable conditions during the training phase and then randomly assigned to one condition during the testing phase. Anxiety was measured with an EMG of the startle eyeblink reflex. The protocol was successfully able to induce fear (predictable condition) and anxiety (unpredictable condition), as measured by eye-blink startle responses during both the testing and training phases. Participants high in cortisol had higher eyeblink startle responses than those lower in cortisol. DHEAS was not related to eyeblink in this sample. Study 2 repeated the protocol, substituting an erotic video during the test phase. Participants were 30 women. In addition to eyeblink, we measured participant genital sexual arousal with a vaginal photoplethysmograph and psychological sexual arousal with a self-report measure. Participants in the unpredictable condition had higher levels of genital arousal and lower levels of psychological arousal compared to participants in the neutral condition. Cortisol levels were significantly negatively related to psychological arousal, but not genital arousal. DHEAS was not significantly related to genital or psychological arousal, but showed a positive correlation with genital arousal. The present study adds to the literature demonstrating that anxiety can increase sexual arousal in women in the laboratory. It also replicates previous findings that cortisol is negatively related to sexual arousal in the laboratory. The high variability in salivary DHEAS data requires larger samples to be able to understand its relationship with anxiety and arousal.

Disclosures: L.D. Hamilton: None. **K.R. Peters:** None. **A.M. Russell:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 068.01/HH28

Topic: F.04. Stress and the Brain

Support: NIDDK grant DK092322

BBRF NARSAD Young Investigator Award to PRB

Title: Personality traits, fitness, and sex impact on psychobiological response to exhaustive acute exercise in adults

Authors: *K. NOWAK[1], K. E. CHAPPELLE[1], A. NEFF[2], P. R. BURGHARDT[1]
[1]Nutr. and Food Sci., Wayne State Univ., Detroit, MI; [2]Psychiatry and Behavioral Neurosci., Wayne State Univ., Clawson, MI

Abstract: Background: Exercise can be beneficial to cognitive function, mental well-being and physical health. Recent evidence suggests that possessing certain personality traits can influence how someone responds to exercise, which can ultimately impact their fitness level, body type, and other physiological parameters. Previous studies have found that gender, ethnicity, and age can influence the extent and directionality of these relationships, with some conflicting and inconclusive results. This study attempts to further elucidate whether specific psychobehavioral traits outlined in the NEO-PI personality test are associated with an individual's emotional and physical response to exercise, and how this relates to their fitness level and various anthropometric measures. **Methods:** Healthy men and women between the ages of 18-65 performed a VO2max test on a treadmill to assess their fitness level. Blood draws were taken prior to, immediately after, 30, 60 and 90 minutes following the test to determine plasma levels of a variety of metabolites, hormones, and cytokines. Subjects completed the NEO-Personality Inventory (NEO-PI) in order to determine how strongly they exhibited five psychobehavioral traits. The POMS and PANAS tests were completed prior to, immediately after and 90 minutes following the VO2max test to determine exercise-induced differences in emotion and mood. **Results:** When comparing NEO-PI scores with measures of fitness and anthropometric data, many of the associations exhibited similar directionality in males and females but in specific instances were more pronounced in one gender. In women, BMI was negatively correlated with extraversion and conscientiousness, but not in men. BMI was negatively correlated with post-exercise changes in tension, however this was only significant in males. Positive affect change displayed a positive trend with resting energy expenditure (REE) in both genders, but the correlation was only significant in males. Men exhibited an inverse association between VO2max and circulating cortisol levels following exercise, however this association was not seen in women. **Conclusion:** These results suggest that the psychological and hormonal

responses to acute exhaustive exercise are influenced by sex, fitness, and personality. This information will be informative for interventions that utilize exercise as an approach to improving health and psychological well-being.

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Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 068.02/HH29

Topic: F.04. Stress and the Brain

Support: NIDDK grant DK092322

BBRF NARSAD Young Investigator Award to PRB

Title: Anterior cingulate cortex glutamate response to emotional stimuli is influence by aerobic fitness

Authors: *P. R. BURGHARDT[1], K. E. CHAPPELLE[1], K. NOWAK[1], A. NEFF[2], D. KHATIB[2], J. A. STANLEY[2]
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Abstract: Effectively coping with stress is a critical skillset that can impact individual health and wellness. Individual traits like neuroticism influence appraisal of emotional stimuli and coping strategies. Fitness is linked to decreased morbidity and mortality, and exercise is known to have a positive impact on stress regulation as well as cognitive and emotional processing. The combination of fitness and psychological traits are likely to influence individual coping strategies as neuroticism has been inversely associated with quality of life in patients with chronic disease and aerobic fitness has shown a protective benefit. The general relationship between aerobic fitness with neuroticism, and the underlying neurobiology, in healthy individuals has not been well described.
Here we begin to investigate the relationship between fitness and neuroticism on the neurobiological response to emotional stimuli. Personality traits and cardiopulmonary fitness were measured in ten health individuals using the NEO Personality Inventory and maximal oxygen consumption (VO_2max), respectively. During a separate visit, in vivo proton functional magnetic resonance spectroscopy (^{1}H fMRS) was used to investigate the modulation of the neurotransmitter glutamate (Glu) in the anterior cingulate cortex (ACC) during an image appraisal task. During ^{1}H fMRS, subjects assessed images from the Nencki Affective Picture System (NAPS) consisting of pictures ranked to have positive (E+), Negative (E-), or neutral

(En) emotional valence.
Trait neuroticism was inversely associated with aerobic fitness. Preliminary analyses indicate that a negative association exists between VO2max and the ACC Glu modulation in response to E-. No association was found between neuroticism and ACC Glu modulation response to any of the stimuli types.
These preliminary results suggest increased aerobic fitness is associated with decreased glutamatergic neurotransmission in the ACC of individuals during appraisal of pictures with a negative emotional valence. These results will help inform treatment strategies for individuals with psychiatric disease.

Disclosures: P.R. Burghardt: None. **K.E. Chappelle:** None. **K. Nowak:** None. **A. Neff:** None. **D. Khatib:** None. **J.A. Stanley:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 068.03/HH30

Topic: F.04. Stress and the Brain

Title: Neuroanatomical correlates of socioeconomic status in young adults: Findings from the Human Connectome Project

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Abstract: BACKGROUND: Socioeconomic status (SES) is a measure of an individual's overall access to financial, human, and social capital. Across the life span SES is associated with physical and mental health, academic and occupational success and other important outcomes. Recent research has correlated children's SES, typically measured by parental income and educational attainment, with brain structure. The largest such study, of 1099 children in the PING data set, found that higher SES children showed larger cortical surface area in number of regions and larger hippocampus and amygdala volumes (Noble et al., 2015, Nature Neuroscience). Few studies have examined SES in young adults and none report SES correlates in comparably large samples, such as the 1,200 young adults of the Human Connectome Project. Do the regions that differ most significantly with SES in the large PING sample (listed below) also differ by SES in the young adults? METHOD: Measuring SES by educational attainment and income (and excluding full-time students whose income is misleadingly low as to their SES), we tested its relation to the following ROIs: Total cortical grey matter, hippocampal and amygdala vols and the surface areas of inferior frontal gyrus, orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex and insula. ANALYSIS: Regressions of SES on

ROIs covaried supratentorial vol, age, race, and gender. To assess the potentially distinctive correlates of income and education, these SES predictors were also analyzed separately. Given the presence of twins and siblings in the HCP sample, and the non-independence of such observations, three subsets were created by sampling one subject from each family resulting in subsets of 411, 295, and 148 subjects. RESULTS: SES was associated with CGM vol in all three subsets (βs = 0.14-0.20, $p<0.001$). In the ROIs based on the child findings, results were uniformly negative except for hippocampal vol, which was associated with SES in the first (β = 0.11, p = 0.02) and third subset (β =0.21, p = 0.01). Consistent with Noble's findings, the hippocampal relation was driven by education rather than income (β = 0.10, p = 0.01 and β = 0.16, p = 0.008, respectively). Concerning laterality, the SES effect was present only on the right (β =0.14, p =0.003; β = 0.23, p=0.01). CONCLUSIONS: This first large study of SES correlates of regional brain anatomy in young adulthood showed that SES affects hippocampal and overall cortical grey matter volume. Future studies will examine additional anatomical regions and measures, and ultimately uncover the mechanisms by which these associations emerge.

Disclosures: B.S. Last: None. **S.T. Jensen:** None. **M.J. Farah:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 068.04/HH31

Topic: F.04. Stress and the Brain

Support: Center for the Study of Traumatic Stress (USUHS)

Center for Neuroscience & Regenerative Medicine (USUHS)

Title: Neurophysiology of aggression in PTSD

Authors: *S. E. SMERIN, H. LI
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Abstract: Background: Traumatic stress in many PTSD patients leads to explosive anger and, all too often, violence. Herein a rat model of fight and flight is utilized toward finding Where in the brain violence foments and How. Where? Areas tested are the ventromedial hypothalamus (VMH), medial amygdala (MeA), and lateral septum (LS), previously implicated in attack, and the hippocampus (HC), since flashbacks and nightmares are fundamental to PTSD. Pyriform cortex (Pyr) is included since olfaction is the rats main sensatory input and is reported by PTSD patients to be the most salient mnemonic evocative of the traumatic experience. A first step toward How is to associate synaptic transmission in and between these regions with behavioral attack.

Methods: Synaptic transmission can be assessed in the behaving rat by recording evoked excitatory postsynaptic field potentials (fEPSP). Coordination between brain regions can be analyzed by recording endogenous local electric field oscillations (ofP) and periodic bursting of action potentials ("rhythmic bursting") of 1-3 Hz (delta), 5-8 Hz (theta), 8-12 Hz (alpha), and 13-30 Hz (beta)) which represent rhythmic synchronous activity of populations of neurons associated with attention and sleep. Procedures included 1) implanting microelectrodes in VMH and MeA for stimulation and in HC, LS, and Pyr for recording fEPSPs, ofPs, and rhythmic bursting, 2) evoking rat attack using the resident/intruder paradigm and theta patterned electrical stimulation in VMH/MeA, 3) recording fEPSPs in response to a continuous probe stimulus along with ofPs and rhythmic bursting, and 4) recording video of attack behavior simultaneous with recorded fEPSPs, ofPs, and rhythmic bursting.
Results: 1) Theta patterned stimulation in VMH/MeA evoked attack in Resident rats challenged with an Intruder rat. In one rat the attacks were delayed by a week, consistent with the delayed onset of symptoms as can occur in PTSD. 2) During the attack, the fEPSP flattened out in HC and LS, then bounced back afterwards. 3) The magnitude, co-occurrence, and correlation of ofPs in LS with mainly rhythmic bursting in HC and Pyr and with behavioral state are complex and recordings still under analysis. 4. As arousal increases from waking through vigilance towards attack the frequency of the ofP in LS appears to increase from slow theta (4Hz) towards beta threshold (13 Hz). 5. ofPs are more prominent during quiet periods after attack than before.
Implications: 1) VMH and MeA are key in evoking attack. 2) HC, LS, and Pyr are active leading up to and following attack, possibly processing "cognitive" information later consolidated during sleep.

Disclosures: S.E. Smerin: None. **H. Li:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

Location: Halls A-C

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Program#/Poster#: 068.05/HH32

Topic: F.04. Stress and the Brain

Support: Divisional and NYMC-Boston Children's Hospital Physician Network Institutional Research Grant

Title: Gut colonization augments the sympathoadrenal capacity to respond to stress

Authors: *B. B. NANKOVA[1], P. GIRI[2], F. HU[3], E. F. LA GAMMA[4]
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Abstract: A diverse range of microbes from the environment colonize the newborn's gastrointestinal tract forming the microbiota - a complex and dynamic ecosystem that has co-evolved with its mammalian host to build a symbiotic relationship. It is now considered to play a critical role in many biological functions in the body including development and function of the central nervous system, in human health and disease. The mutually beneficial relationship between the host and gut microorganisms arises in part from short chain fatty acids (SCFAs) which are produced from bacterial fermentation of some proteins, dietary carbohydrates and oligosaccharides. In addition to their direct effects on gastrointestinal physiology, SCFA may affect brain and behavior by multiple epigenetic mechanisms. We have shown before that SCFA can regulate catecholamine biosynthesis *in vitro* and *in vivo*. How gut microbes affect the adrenal component of the sympathetic nervous system is not known and the evidence relating abnormal gut function to maladaptive responses to stressors is limited. Here we explored the potential link between gut microbiota/gut-derived signals and sympathoadrenal stress responsivity in germ free (GF) mice. The effect of insulin-induced hypoglycemia was compared in young adult control (colonized) mice and mice lacking microbiome (GF). A group of control mice kept for one week under sterile conditions (diet, water, cages) was also included to account for potential effects of the environment. The animals from each experimental group were randomly divided into saline treated and insulin treated subgroups. Blood glucose levels were monitored from tail nick samples to ensure development of hypoglycemia. The GF animals exhibited significantly lower basal urine epinephrine levels. Although unable to mount epinephrine response to hypoglycemia GF mice showed similar to control mice corticosterone (intact hypothalamic-pituitary-adrenal cortical axis) and glucagon (intact parasympathetic neuronal axis) release. No SCFA were detected in the caecum of GF mice. Housing colonized mice in sterile conditions altered the SCFA profile, consistent with an altered microbiome composition. Of note, gender specific differences were observed for propionate. These results provide a proof of concept, that gut microflora and perhaps SCFA are essential for establishing catecholamine homeostasis under basal and stimulated conditions. We speculate that postnatally acquired gut flora represent a symbiotic evolutionarily distinct survival advantage to newborns enabling better adaptation to common stressors such as hypoglycemia, cold and hypotension.

Disclosures: B.B. Nankova: None. **P. Giri:** None. **F. Hu:** None. **E.F. La Gamma:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Topic: F.04. Stress and the Brain

Support: NIH Grant EY019049

NIH Grant DC008983

Title: Zona incerta bi-directionally modulates defense behaviors

Authors: *X. CHOU[1,2], X. WANG[1,2], Z. ZHANG[1,5], B. ZINGG[1,2], J. HUANG[1], L. MESIK[1,2], W. ZHONG[1,5], H. W. TAO[1,3], L. I. ZHANG[1,4]
[1]Zilkha Neurogenetic Inst., Los Angeles, CA; [2]Neurosci. Grad. Program, [3]Dept. of Cell and Neurobiology, Keck Sch. of Med., [4]Dept. of Physiol. and Biophysics, Keck Sch. of Med., USC, Los Angeles, CA; [5]Dept. of Physiol., Southern Med. Univ., Guangzhou, China

Abstract: Defense behaviors are important for animal survival. How these behaviors are modulated according to experience and environment remains largely unknown. In this study, we identified a novel pathway from rostral subdivision of ZI (ZIr) to periaqueductal gray (PAG) regulating both innate noise-induced flight responses and conditioned freezing. Optogenetic activation or inactivation of ZIr could either suppress or enhance both defensive behaviors. In addition, activating the projection from ZIr to PAG directly could reduce the defensive behaviors. Interestingly, we found ZIr activity would progressively increase during fear extinction training, and silencing infralimbic area (ILA) eliminated the increase. Overall, our data demonstrate that ZIr can bi-directionally modulate both innate and learned defense behaviors, and implicate a role of the ILA-ZIr projection in facilitating fear extinction along with other known circuits.

Disclosures: X. Chou: None. **X. Wang:** None. **Z. Zhang:** None. **B. Zingg:** None. **J. Huang:** None. **L. Mesik:** None. **W. Zhong:** None. **H.W. Tao:** None. **L.I. Zhang:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Topic: F.04. Stress and the Brain

Support: DA09082

DA 020129

DA08259

Title: Ultrastructural analysis of estrogen receptor alpha, corticotropin-releasing factor type 1 receptor and norepinephrine in female locus coeruleus

Authors: *B. A. REYES[1], M. URQUHART[1], J. ZHANG[1], T. A. MILNER[2], E. J. VAN BOCKSTAELE[1]

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Abstract: Stress-related psychiatric disorders, including anxiety and depression, present a challenge to women's health because women are twice as likely as men to suffer from these psychopathologies. One of the features of stress-related psychiatric disorders in both sexes is the dysregulation of noradrenergic neurotransmission. The brainstem locus coeruleus (LC) contains the largest cluster of noradrenergic neurons and projects to the entire neuraxis. Dysregulation of cortical norepinephrine (NE) levels has been linked to the pathophysiology of stress-related psychiatric disorders. Corticotropin-releasing factor (CRF) mediates stress-related activation of the LC-NE system via modulation of the CRF type 1 receptor (CRFr) that in turn increases NE release in target nuclei, including the cortex. Sex differences have been reported in CRFr signaling in the LC. Estrogens have been reported to be involved in these observed sex differences, but the mechanism of how estrogen affects these non-reproductive brain functions remains to be elucidated. Estrogen exerts its actions by binding to the estrogen receptor alpha (ERα), beta, and GPER1. In the present study, we investigated ultrastructural substrates underlying putative interactions between ERα, CRFr and NE in the LC using immunoperoxidase and dual immunogold electron microscopy. Forty-micron thick sections of female Sprague Dawley rats were collected from the LC and processed for immunocytochemical detection of ERα, CRFr and tyrosine hydroxylase (TH). Our preliminary data are consistent with our previous report showing that ERα-immunoreactivity (ir) is localized predominantly in somatodendritic processes of LC neurons. The present findings expand on these studies by showing that CRFr is expressed in dendrites that also contain ERα-ir and TH-ir. In some cases, ERα-ir was identified on axon terminals forming synaptic contacts with dendrites exhibiting CRFr and TH labeling. These results indicate that CRFr may directly affect the neuronal activity of ERα-responsive noradrenergic neurons and that estrogen may influence the activity of CRFr expressing neurons in the LC.

Disclosures: B.A. Reyes: None. **M. Urquhart:** None. **J. Zhang:** None. **T.A. Milner:** None. **E.J. Van Bockstaele:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Topic: F.04. Stress and the Brain

Support: Canadian Institutes of Health Research (MOP136840)

Title: HPA axis and serotonin (5-HT) 1A receptor responses to repeated restraint stress in male and female rats

Authors: *T. J. PHILIPPE, A. FERLAND, J. CHANG, Y. YANG, V. VIAU
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Abstract: Most basic research on the behavioural and neural consequences of homeostatic threat has been conducted in male subjects only, despite marked sex disparities in the incidence of mood-related disorders associated with stress. As with several neurotransmitter systems, serotonin (5-hydroxytryptamine; 5-HT) expression and signaling is sexually dimorphic in unstressed animals, as well as in those exposed to repeated challenges. Our previous findings suggest that males and females differentially rely on the 5-HT 1A receptor subtype to regulate the recruitment of 5-HT synthesizing neurons in dorsal raphe nuclei, at least under acute stress conditions. Thus, we reason that changes in 5-HT activity may also come to explain underlying sex differences in stress HPA axis habituation, defined as a reduction in glucocorticoid responses to the same stimulus repeated in a predictable manner. Patterns of HPA axis habituation (corticosterone) in response to 5 daily episodes of 2h restraint stress exposure were compared in adult male and female Sprague-Dawley rats. After repeated restraint, separate cohorts were injected with the 5-HT 1A receptor agonist, 8-hydroxy-2-[di-n-propylamino]tetralin (8-OH-DPAT), using hypothermia and corticosterone responses as physiological indices for changes in central pre- and postsynaptic 5-HT 1A receptor function, respectively. Although females showed higher absolute levels of corticosterone than males under acute and repeat conditions, males and females displayed similar declines in total hormone responses between the first and last bout of restraint (45 and 40 %, respectively). As a function of repeated restraint, corticosterone responses to 8-OH-DPAT were potentiated in both males and females; whereas hypothermia was induced only in males. Since 5-HT normally activates the HPA axis, increases in 5-HT 1A receptor sensitivity at postsynaptic sites may play a role in the maintenance or formation of stress adaptation in both males and females. However, only males showed increases in presynaptic 5-HT 1A receptor responses, which normally diminishes excitability of 5-HT raphe neurons. Taken together, despite showing similar capacities for stress habituation, this process may nonetheless require distinct underlying changes in 5-HT synthesis, release and signal transfer in males and females.

Disclosures: T.J. Philippe: None. **A. Ferland:** None. **J. Chang:** None. **Y. Yang:** None. **V. Viau:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Topic: F.04. Stress and the Brain

Support: NIH Grant MH103322

Title: Kappa opioid receptors in dorsal raphe increase aggression in California mice

Authors: *E. C. WRIGHT[1], I. E. DOIG[1], C. JAMARILLO[1], A. LAMAN-MAHARG[2], B. C. TRAINOR[1]
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Abstract: The dorsal raphe nucleus (DRN) is an important site of kappa opioid receptor (KOR) action, the activation of which leads to down regulation serotonergic release. Other studies examining this mechanism have been conducted on male rodents, but this study examines effects in both males and females. Previous data from our lab showed that exposure to social defeat stress increased tryptophan hydroxylase (TPH)/phospho extracellular signal regulated kinase (pERK) colocalizations in the DRN of females (n=5-8, p=<0.01), and males (n=7-8, p<0.01). Intraperitoneal injection with U50,488 reduced this effect, to a greater extent in females than males, suggesting that KOR may normalize serotonergic release in stressed animals. Here, we examined the effect of U50,488 infusions in the DRN in mice exposed to social defeat or control conditions. Male and female California mice underwent three consecutive days of social defeat (or control condition), and one week later were implanted with a cannula guide into DRN. After 6 days of recovery mice were injected with a low (0.25ug) or high (0.50ug) dose of U50,488 (a KOR agonist) or artificial cerebrospinal fluid control. Thirty minutes later mice were tested via social interaction test. The next day the same process was repeated for a resident intruder test. Preliminary results show that U50,488 increases offensive aggression in aggression within the stress naïve males (n=4 per group, $p < 0.05$). In stressed females U50,488 increases defensive aggression (n=4 per group, $p < 0.05$). U50,488 had weak effects in the social interaction test. These results indicate that the effects of KOR in the DRN are context dependent and may reverse some aspects of stress-induced behavioral phenotypes.

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Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: F.04. Stress and the Brain

Support: NIH R01 MH050479

Title: Diurnal variation of the effect of an acute stressor on an anxiety-like behavior

Authors: *J. R. RAVENEL, R. A. DAUT, L. K. FONKEN, L. R. WATKINS, S. F. MAIER
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Abstract: Several psychiatric disorders can be elicited or exacerbated by the experience of stressful life-events. Stress exposure can alter normal physiology and result in a variety of behavioral changes that have been successfully replicated with animal models. Since individuals respond differently to stressful experiences and there appears to be a large variability in stress susceptibly among the population, it is important to understand factors that underlie these differences. When rats are exposed to inescapable stress (IS) through a series of tail shocks (100, 5 sec, 1.3-1.6 mA), the mid-to-caudal region of the dorsal raphe nucleus (DRN) is robustly activated. This results in a pronounced release of extracellular serotonin (5-HT) within the DRN and its projection regions, such as the basolateral amygdala (BLA). The excess extracellular 5-HT desensitizes 5-HT1_a inhibitory auto-receptors within the DRN resulting in sensitization of the activity of these neurons. This sensitization allows future activation of this circuit to result in exaggerated 5-HT release in the BLA, which is thought to mediate stress-induced anxiety that manifests in reduced juvenile social interaction behavior. The DRN neurons that become sensitized are under circadian control and DRN 5-HT release in rats fluctuates diurnally; therefore we sought to determine whether diurnal variations in stress susceptibility exist. Rats that were exposed to IS during the middle of their active phase (ZT16) did not show the expected reduction in juvenile social interaction behavior typically seen 24 hours later in animals stressed in the middle of their inactive phase (ZT6). Absolute corticosterone concentrations did not differ immediately or 24 hours after stress, however stress at ZT16 resulted in significantly greater activation of middle-DRN 5-HT neurons relative to ZT6. While these results suggest that an IS-induced anxiety-like behavior is time of day dependent, they do not supply a clear mechanism for the diurnal variations. Since it appears as if rats are more susceptibly to stress during their inactive phase, these results have important implication for people who largely experience stress during their inactive phase, such as shift-workers. Ongoing experiments are aimed at assessing cell-type specific activation within the BLA to determine if the proximal mediator of this activity exhibits a diurnal response to stress exposure.

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Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Fulbright Garcia-Robles Fellowship

Title: Neurosteroid-producing inputs to estrogen receptor-bearing lateral habenular neurons

Authors: *L. E. EIDEN[1], V. S. HERNANDEZ[2], L. ZHANG[1,2]
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Abstract: Sexual and other hedonic behaviors associated with species survival sometimes compete with behaviors associated with individual survival, such as the seeking of food, water, or safety. The habenula, situated in the epithalamus, is proposed as a circuit nexus for mediating value-based decision making in such situations. Understanding how environmental information that contributes to habenular decision-making is conveyed to the habenula, and how it is conditioned by sexual, environmental, and homeostatus, requires specific knowledge about the neurochemistry and microanatomy of habenular inputs. We have identified a subnucleus of the lateral habenula, in its mediocentral aspect (LHbMC), that is characterized by a high concentration of GABAergic neurons expressing the estrogen receptor ERalpha, some of which possess dual projections within the LHbMC, and projecting from it. This 'subnucleus' receives major afferents from the hypothalamus, including orexinergic neurons of the lateral hypothalamus, and vasopressinergic neurons of the paraventricular nucleus of the hypothalamus, and from brain stem/midbrain aminergic nuclei, including the dorsal raphe and ventral tegmental area. To investigate the possibility that sex-related endocrine status impinges upon this circuit subunit of convergent inputs on the GABAegic estrogen-receptive neurons of the LHbMC, we investigated whether or not any or all of these inputs are equipped to synthesize estrogen locally, or to respond to variations in sex steroids with a potentially altered local output of neurosteroids within the LHbMC. All four inputs, two peptidergic and two monoaminergic, were found to express, in addition to their metabotropic neurotransmitters, androgen receptors, as well as the P450 androgen reductase CYP19A1 (aromatase; estrogen synthase), which confers the ability to aromatize the androgens androstenedione and testosterone to estrone and estradiol, both ligands for ERalpha. In particular, aromatase expression was found by immunohistochemistry to be quite prominent not only in cell bodies of projection neurons, but in their nerve terminals within LHbMC. Related to a potential role for aromatase and estrogen signaling to habenula-related behaviors, we have found that escape and freezing behaviors initiated by predator proximity in male rats is enhanced by removing peripheral testosterone by castration.

Disclosures: L.E. Eiden: None. **V.S. Hernandez:** None. **L. Zhang:** None.

Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Neuroendocrinology Charitable Trust 297693 Award to NRP

Title: Circadian expression of tryptophan hydroxylase 2 in the dorsal raphe nuleus and the median raphe nucleus is altered by dysregulated glucocorticoid rhythms

Authors: *N. M. REYES PRIETO[1], Y. KERSHAW[1], B. BENNET-LLOYD[1], J. E. HASSELL, Jr[2], T. GRACIE[2], C. A. LOWRY[2], B. L. CONWAY-CAMPBELL[1], S. L. LIGHTMAN[1]
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Abstract: Stress-related psychiatric disorders are characterized by dysregulated activity of both the hypothalamic-pituitary-adrenal axis (HPA axis) and serotonergic systems. However, the exact nature of the relationship between these systems remains unknown. In particular, it is unclear whether dysregulation of the HPA axis is the cause or the effect of anomalies in serotonergic systems. We hypothesized that the activity of the HPA axis has an important role in the regulation of expression of *tph2* mRNA, encoding tryptophan hydroxylase 2, the rate-limiting enzyme in the biosynthesis of serotonin, and, therefore, has an important role in regulation of serotonergic systems. To test this hypothesis, we studied three experimental conditions designed to alter the circadian rhythm of HPA axis activity in rats: 1) normal control conditions, 2) administration of the long-acting synthetic glucocorticoid methylprednisolone (MPL) at a dose of 1mg/mL provided *ad libitum* in drinking water for 5 days, and 3) constant exposure to 200lux light for 5 weeks (L:L). To evaluate the effects of these manipulations we took whole brains and trunk blood from 9-week-old male Sprague-Dawley rats (n=8 per time per group) at defined times over a 24 hour period (circadian time (CT)2, CT8, CT11, CT14, and CT20). Radioimmunoassays (RIA) were used to assess plasma corticosterone (CORT) levels and *in situ* hybridization histochemistry (ISHH) was used to evaluate *tph2* mRNA expression throughout the dorsal raphe nucleus (DR). Relative to control rats, MPL-treated rats showed a suppressed circadian rhythm of plasma CORT, while L:L rats showed hyperactive CORT secretion with high amplitude CORT levels detected throughout the 24 hour period. The ISHH analyses revealed a circadian rhythm of *tph2* expression in the control rats, with the lowest expression detected at CT2. *Tph2* mRNA rose rapidly throughout the timecourse, with highest expression levels detected at CT8, CT11 and CT14, decreasing towards baseline at CT20. Interesting, this circadian profile of *tph2* mRNA expression was altered by both MPL treatment and L:L exposure. Strikingly, the caudal region of the ventral DR (DRV) was particularly responsive to both interventions. The circadian *tph2* variation was less pronounced in the MPL-treated rats, with an overall flattening of the profile over the 24 hour period. Interestingly, circadian *tph2* rhythm was more pronounced, and phase-shifted by 6 hours, in L:L rats compared to control rats. These striking changes in the daily rhythmic expression of *tph2* might have significant

implications for serotonin biosynthesis in the DR, which in turn would impact upon the serotonergic system and affective state.

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Poster

068. Stress-Modulated Pathways: Cortex to Brainstem

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Program#/Poster#: 068.13/II4

Topic: F.04. Stress and the Brain

Title: A role for galanin transmission in central respiratory chemoreception following acute and chronic respiratory challenge

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Abstract: Glutamatergic chemoreceptor neurons in the retrotrapezoid nucleus (RTN) form extensive projections to the ventral respiratory column (VRC), which generates the rhythmic breathing pattern. RTN chemoreceptors are critically involved in mediating the central respiratory chemoreflex, which is the primary homeostatic mechanism used by mammals to control blood CO_2 levels. Although glutamate is the primary transmitter used to excite the VRC (Holloway BB *et al* 2015, Ruffault PL *et al* 2015), 50% of RTN neurons in the rat also express the inducible neuropeptide transmitter galanin (Stornetta *et al* 2009, Spirovski *et al* 2012). Previous studies have demonstrated that injection of galanin into the VRC has an inhibitory effect on breathing, inducing apnoea (Abbott SB *et al* 2009). Importantly galanin also attenuated the ventilatory reflex responses to hypoxia and hypercapnia (elevated CO_2). We hypothesise that RTN galanin signalling acts as a gain-control mechanism for the central chemoreflex, and that neuropeptide expression is regulated by environmental signals (such as blood pH). We aimed first to determine the distribution of preprogalanin (ppGal) mRNA in the mouse RTN using in situ hybridisation (ISH). We also aimed to determine whether ppGal mRNA expression is altered in the RTN, VRC or cerebellum following hypoxic or hypercapnic respiratory challenge. Chronic intermittent hypoxia challenge: Rat pups (p7) were divided into normoxia (control, 21%O_2/79% N_2) and intermittent hypoxia (IH, 8% or 12% O_2, balance N_2) groups. Rat pups in IH groups were exposed to a hypoxic environment for an hour each day, for 5 days. Short term hypercapnia challenge: Adult mice were divided into normoxia (control , 0% CO_2) and hypercapnia (5% CO_2, balance room air) groups. Mice in the hypercapnia group were exposed to a single 5% CO_2 challenge for 3, 6 or 8 hours. Following the challenge, animals were euthanized

and fresh tissues (RTN, VRC, and cerebellum) were isolated. We assessed changes in gene expression with quantitative PCR (QPCR). The ISH results show that ~30% of mouse RTN neurons are galaninergic (ppGal+). QPCR results show that there was no significant change in RTN ppGal mRNA levels following IH (12% O_2), however, ppGal was upregulated 2-fold in the RTN and 3-fold in the VRC following IH (8% O_2), compared to normoxia. Preliminary data suggests that ppGal mRNA is downregulated in the RTN following a 3, 6 and 8 hour hypercapnia challenge, compared to control conditions. Overall, our data suggest a role for galanin transmission in RTN chemoreception following acute and chronic respiratory challenges, which occur in respiratory syndromes including COPD and sleep apnea.

Disclosures: N.N. Kumar: None. **A.S. Dereli:** None. **D.A. Bayliss:** None. **N.M. Jones:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.01/II5

Topic: F.04. Stress and the Brain

Title: Examination of cortisol receptor and endogenous opioid expression in a primate model of self injurious behavior

Authors: *M. JACKSON[1], B. FORET[3], K. M. SMITH[2], J. A. FONTENOT[4], E. C. ROMERO[4], J. A. SMITH[4], D. L. HASSELSCHWARTZ[4]
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Abstract: Abstract
Suicide is the tenth leading cause of death in the United States, the second leading cause of death for those between the ages of 15 to 24, and accounted for approximately 41,000 deaths in the year 2014. It is important to understand the underlying mechanisms that may lead a person to self harm. Non-suicidal self-injury (NSSI) is the deliberate infliction of physical harm to one's own body without suicidal intent. While NSSI is by definition, not an attempt at suicide, it is strongly associated with future suicide ideation and has been described as a "gateway" behavior. Self-injurious behavior occurs in approximately 1-4% of the adult human population. SIB also occurs in a low percentage of captive monkeys. Rhesus Macaque monkeys are evolutionarily and physiologically similar to humans, share 93% of their DNA with humans, and consequently, have long been used as testing subjects for vaccine and clinical trials. In order to study SIB we used 8 sex-matched pairs of rhesus macaques, eight who exhibited self-injurious behavior (SIB) and eight controls, to examine alterations in gene expression. The brain regions chosen are those closely linked to reward reinforcement and stress adaptation including the hypothalamus, orbital frontal cortex, nucleus accumbens, hippocampus, caudate, putamen and the amygdala. Previous

studies have identified reactive changes in astrocytes of animals exhibiting SIB. We have therefore collected fourteen additional rhesus macaques, nine who exhibited SIB, to examine morphological changes in astrocytes. We observed a significant downregulation of the mineralocorticoid receptor (MR) with no change in glucocorticoid receptor (GR) in the amygdala of female rhesus macaques exhibiting SIB. A significant upregulation of GR, but not MR was found in the amygdala of males with SIB. The amygdala has projections to the hypothalamus, regulating the release of CRF, therefore an increase in GR binding in the amygdala likely increases the production and release of CRF by the hypothalamus. In the hippocampus of females with SIB, we observed a reduction in GR and an increase in MR. Thus far, our findings suggest no uniform significant changes in the gene expression of the mu-opioid receptor, β-endorphin precursor molecule proopiomelanocortin (POMC), or the dynorphin A and B precursor prodynorphin, although individual animals have disruptions compared to their matched controls. Previous studies have hypothesized that altered endogenous opioid expression occurs in the brains of individuals and animals that self-injure. Our studies indicate the need for further studies to identify if, and how this is occurring in self-injuring macaques.

Disclosures: M. Jackson: None. **B. Foret:** None. **K.M. Smith:** None. **J.A. Fontenot:** None. **E.C. Romero:** None. **J.A. Smith:** None. **D.L. Hasselschwartz:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.02/II6

Topic: F.04. Stress and the Brain

Support: NIMH K01MH102406

Title: Multimodal characterization of the stria terminalis and its bed nucleus: Childhood maltreatment-related phenotypes of mood and anxiety vulnerability

Authors: *L. BANIHASHEMI[1], C. W. PENG[3], T. D. VERSTYNEN[4], M. L. WALLACE[2], H. AIZENSTEIN[2], A. GERMAIN[1]
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Abstract: The bed nucleus of the stria terminalis (BST) is a central visceral “hub” in the control of stress responses. The amygdala and BST are heavily interconnected, while the BST densely and directly innervates the paraventricular nucleus of the hypothalamus (i.e., the apex of the HPA axis). The white matter of the stria terminalis (ST) connects this stress-control network. Childhood maltreatment dysregulates later stress reactivity, yet how maltreatment alters stress-control structures is unclear. Previously, we have shown that sub-severe levels of childhood

physical abuse predict greater stressor-evoked BST reactivity in healthy adults (Banihashemi et al., SCAN, 2014). Here, our goal was to examine childhood maltreatment-related differences in ST structural integrity and BST stress reactivity in a mixed sample, while considering how one's inherent mood/anxiety vulnerability may drive these effects. Participants included young adults (n=70, 43 females; mean age = 27.8, SD = 3.8) with a full range of maltreatment severity and mood/anxiety symptoms. 'Resilient' individuals (n=24) have *never* had a mood/anxiety disorder diagnosis, while 'vulnerable' individuals (n=46) have *any* history of mood/anxiety disorder. The Childhood Trauma Questionnaire (CTQ) provided an assessment of childhood maltreatment (i.e., abuse and neglect). Participants underwent a 271-direction diffusion spectrum imaging sequence and performed a mild cognitive stress task (i.e., the multisource interference task) in the MRI scanner. Structural integrity (i.e., quantitative anisotropy) measures were extracted from a ST tract defined by tractography with Human Connectome Project data. BST stress reactivity measures are parameter estimates from the contrast between task control and stress conditions extracted from a hand-drawn region of interest. 'Resilient' individuals display a positive (albeit non-significant) relationship between childhood maltreatment and ST structural integrity (r = .236, p = .267), while 'vulnerable' individuals display a significant negative relationship (r = -.302, p = .041). Further, resilient individuals display a significant positive relationship between childhood maltreatment and BST stress reactivity (r = .426, p = .038), indicating greater BST reactivity, whereas there is no such relationship among vulnerable individuals (r = .083, p = .582). Our findings indicate differential maltreatment-related ST and BST "phenotypes," whereby ST strengthening (resilience) or weakening (vulnerability) may determine whether appropriate neural and physiological stress responses can be mounted and may also predict current mood/anxiety symptoms.

Disclosures: L. Banihashemi: None. **C.W. Peng:** None. **T.D. Verstynen:** None. **M.L. Wallace:** None. **H. Aizenstein:** None. **A. Germain:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.03/II7

Topic: F.04. Stress and the Brain

Support: NIMH Grant 109975

Title: Sex- and age-dependent effects of orexin 1 receptor blockade on open field behavior and neuronal activity

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Abstract: Adolescence is a sensitive and critical period in brain development where psychiatric disorders such as anxiety, depression and post-traumatic stress disorder are more likely to emerge following a stressful life event. Females are two times more likely to suffer from psychiatric disorders than males. Patients with these disorders show alterations in orexins (also called hypocretins), important neuropeptides that regulate arousal, wakefulness and the hypothalamic-pituitary-adrenal axis activity. The role of orexins in mediating arousal behaviors in male and female rats during adolescence or adulthood is not known. Here, we examine the influence of orexin 1 receptor blockade (SB334867) in open field behavior in male and female rats during adolescence (PD 31-33) or adulthood (PD 75-77). Animals were injected with 0 (vehicle),1,10, or 30mg/Kg SB334867 (i.p.). Open field behavior and neuronal activity (c-Fos) were assessed. In adolescent males, SB334867 significantly increased immobility in 10mg/Kg group compared to vehicle, and the drug-induced increase in immobility was associated with increased c-Fos immunoreactivity in the central amygdala. However, this drug effect was not observed in adolescent females. Adolescent males in the 10mg/Kg dose group spent more time immobile compared to the adolescent females in the same dose group. In contrast to adolescent males, adult males in the 10mg/Kg dose group showed reduced immobility. Using immobility as a measure of arousal, these results indicate that 10mg/Kg dose of SB334867 has opposing effects in adolescent and adult males, but few effects in adolescent and adult females. Collectively, our results suggest orexin 1 receptor expression and/or function has a sex-specific developmental maturation in rats.

Disclosures: S.R. Blume: None. **H. Nam:** None. **S. Luz:** None. **S. Bhatnagar:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.04/II8

Topic: F.04. Stress and the Brain

Support: R01MH109975

Title: Orexins and sex differences in stress-induced cognitive and sleep deficits

Authors: *L. GRAFE[1], S. LUZ[1], S. BHATNAGAR[2]
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Abstract: Women are twice as likely as men to suffer from stress-related psychiatric disorders, such as post-traumatic stress disorder (PTSD) and depression, however, the biological basis of these sex differences is unknown. Key features of these disorders include sleep disturbances, Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation, and cognitive deficits. The

neuropeptides orexins, known to underlie arousal, the stress response, and attention, are altered in anxious and depressed patients. We recently found that female rats have increased orexin expression and activation compared with males, leading to impaired HPA habituation to repeated stress and subsequent cognitive deficits in an operant strategy shifting test. We then asked whether differential activation of orexin neurons in females compared to males could underlie the lack of habituation and subsequent cognitive deficits in female rats. Data indicated that inhibiting orexin neurons (via Designer Receptors Exclusively Activated by Designer Drugs; DREADDs) during repeated restraint decreased activation in the PVN, decreased basal corticosterone levels, and improved subsequent cognitive function in females. Besides stress-induced cognitive deficits, it is likely that high orexins in combination with stress could underlie sleep disturbances, which are more common in women. Using telemetry devices, we found that repeated restraint stress caused sleep disruptions in female rats but not male rats. Specifically, REM sleep duration and bouts were suppressed in females during five days of 30-min repeated restraint stress and this persisted during a two day recovery period. Moreover, wake duration was higher in females during repeated restraint stress and recovery. We are currently using DREADDs to inhibit orexins throughout repeated restraint to see if we can reverse these stress-induced sleep disturbances in females. As orexins regulate stress responses, cognitive function, autonomic responses, and emotional memory, targeting orexins may impact a range of psychiatric symptoms in a sex-specific manner.

Disclosures: L. Grafe: None. **S. Luz:** None. **S. Bhatnagar:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.05/II9

Topic: F.04. Stress and the Brain

Support: RO1 MH105528

Title: Uncoupling the sensory and affective components of chronic neuropathic pain

Authors: *T. PARETKAR[1], E. DIMITROV[2]
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Abstract: The central nucleus of the amygdala (CeA) plays an important role in anxiety and nociception. We injected viral constructs expressing excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) into the CeA of ENKcre transgenic mice and investigated the effects of acute and prolonged excitation of amygdala enkephalinergic (ENK) neurons on neuropathic pain and affective behavior. Acute activation of excitatory DREADDs expressed by ENK neurons in CeA increased the time spent in open arms of Elevated O-maze

(O-maze) (t_9=2.5, $p<0.05$). In addition, the acute activation of ENK neurons decreased the mechanical allodynia in mice with neuropathic pain (t_{13}=3.22, $p<0.05$) and decreased time to feed in the novelty suppressed feeding (NSF) test (t_{13}=2.2, $p<0.05$). Prolonged excitation of ENK neurons for 14 days also relieved mechanical allodynia (t_{17}=5.4, $p<0.0001$). Next, we evaluated hippocampal neurogenesis in mice by assessing the expression of proliferating cell nuclear antigen (PCNA-ir) and doublecortin (DCX-ir). Persistent pain decreased the expression of PCNA and DCX in the hippocampus but prolonged activation of the amygdala ENK neurons recovered somewhat PCNA and DCX expression in mice with neuropathic pain (PCNA-ir, t_{11}=2.7, $p<0.05$; DCX-ir, t_{18}=5.8, $p<0.0001$). Surprisingly these mice demonstrated an increase of time to feed in the NSF test (t_{17}=5.4, $p<0.0001$), which is a sign for anxiety- and depression-like behavior. Next, we activated ENK neurons in uninjured mice. Prolonged activation of CeA ENK neurons also led to increased anxiety- and depression-like behavior as measured by O-maze and NSF (O-maze, t_{17}=3.7, $p<0.05$; NSF test t_{22}=3.4, $p<0.05$). The dorsal subnucleus of the dorsal raphe (DRD), which is implicated in the control of anxiety responses and pain modulation, showed an increased expression of ΔFosB-ir in mice with prolonged activation of amygdala ENK neurons (t_{10}=6.3, $p<0.001$). Our experiments showed that while acute excitation of ENK neurons in CeA causes anxiolysis in both injured and uninjured mice, prolonged excitation of ENK neurons increases anxiety- and depression-like behavior in both injured and uninjured mice. The brain circuitry that underlines the analgesic and behavior effects of the amygdala ENKergic neurons very likely includes the serotonin system, more specifically the DRD.

Disclosures: **T. Paretkar:** None. **E. Dimitrov:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

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Program#/Poster#: 069.06/II10

Topic: F.04. Stress and the Brain

Support: NIH Grant AA024439

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NIH Grant DA030425

Title: The pituitary adenylate cyclase-activated polypeptide (PACAP)/PAC1 receptor system of the central amygdala mediates the behavioral outcomes of chronic social defeat stress in rats

Authors: *M. SEIGLIE, C. VELAZQUEZ-SANCHEZ, P. COTTONE, V. SABINO
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Abstract: Stress is one of the main contributing factors for both the onset and the maintenance of anxiety and depressive disorders. Interestingly, only certain individuals are vulnerable to the effects of stress and develop psychopathologies, while others remain resilient. The mechanisms underlying stress resilience and vulnerability remain not fully understood and this gap significantly delays the advancement of the biomedical sciences. Identifying the role of specific extrahypothalamic neuropeptides in the pathological response to stress could lead to novel treatments for either enhancing resilience or mitigating susceptibility. Pituitary adenylate cyclase-activating polypeptide (PACAP), a 38-amino acid peptide, and its receptor PAC1R, have been proposed to regulate the stress response in the central amygdala (CeA) and there dysregulation may contribute to the etiology of anxiety, trauma-related and depressive disorders. Here we used the chronic social defeat paradigm which produces a depressive-like symptomatology of attenuated body weight gain, increased anhedonia, and heightened anxiety-like behavior. We found that chronic social defeat stress produced a significant increase in PACAP and PAC1R expression levels in the central nucleus of the amygdala (CeA) compared to control unstressed rats. To assess the functional role of these alterations in the PACAP/PAC1R system of the CeA in the depressive- and anxiety-like symptomatology caused by the exposure to chronic social defeat stress, PAC1R was knocked down in the CeA of control and chronic defeat animals via microinjections of a short hairpin RNA adeno-associated virus (AAV-shPAC1R). Knockdown of PAC1R in the CeA significantly blunted the reduction in body weight gain, reduced anhedonia, and decreased anxiety-like behavior in chronic social defeat animals, while it had no effect on controls. Our data strongly suggest that the dysregulation of the PACAP/PAC1R system of the CeA stress may mediate the behavioral outcomes of chronic social defeat stress and propose this system as a novel target for medications to treat anxiety and mood disorders.

Disclosures: M. Seiglie: None. **C. Velazquez-Sanchez:** None. **P. Cottone:** None. **V. Sabino:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.07/II11

Topic: F.04. Stress and the Brain

Support: Department of Veterans Affairs Merit Review Grant # BX00155605

Title: Chemogenetic silencing of crf neurons in paraventricular nucleus partially restores homeostatic responses to chronic sleep restriction

Authors: *S. KUMAR[1], K.-C. HSIEH[1,2], D. MCGINTY[1,3], R. SZYMUSIAK[1,2,4]
[1]Veteran Affairs Med. Ctr., Los Angeles, CA; [2]Med., [3]Psychology, [4]Neurobio., UCLA, Los Angeles, CA

Abstract: Introduction: Homeostatic responses to sleep loss occur following 1-2 days of sleep restriction, but are attenuated following chronic sleep restriction (CSR). CSR can be viewed as a chronic stress, and we hypothesized that activation of corticotropin releasing factor (CRF) neurons in the hypothalamic paraventricular nucleus (PVN) contributes to the attenuation of sleep homeostasis during CSR. We examined the effects of chemogenetic silencing of CRF neurons in the PVN on sleep and EEG measures during CSR in mice.
Methods: 5 male CRF-ires-Cre mice received bilateral injections of pAAV-hSyn-DIO-M4D(Gi)-Cherry targeting the PVN and were implanted with EEG/EMG electrodes. For CSR, mice were housed in plastic recording cages suspended above the belt of a treadmill. Three weeks after viral vector injections and adaptation to the treadmill cage, a 24 hr baseline sleep-wake and EEG was recorded. To achieve CSR, the treadmill was activated for 3 sec (2cm/sec) followed by 12 sec off. This sequence was repeated for 3 hrs, after which mice were provided a 1 hr of sleep opportunity with the treadmill off. This 3:1 hr schedule was applied continuously for five days. Intraperitoneal injections of vehicle (days 3 and 5) or clozapine-n-oxide (CNO; 10 mg/kg; day 4), were administered at zeitgeiber time (ZT) 07. EEG slow-wave activity (SWA) in nonrapid eye movement (NREM) sleep (expressed as % change from baseline values), total sleep time (TST) and NREM sleep bout duration were quantified during the 1 hr sleep opportunity at ZT9-10.
Results: During 1 hr sleep opportunities at ZT9, TST increased from 36.0±1.5 min at baseline to 42.1±2.0 min on day 1 of CSR. After vehicle injection on CSR days 3 and 5, TST averaged 38.6±2.7 min and 37.7±2.2 min, respectively. On day 4 following CNO injection, TST increased to 42.6±1.7 min. A similar pattern was observed for EEG SWA. On day 1 of CSR, SWA in NREM sleep averaged +55.8±11.2% of baseline levels. After vehicle injection on days 3 and 5, EEG SWA averaged +18.1±7.9% and +17.1±6.5% of baseline, respectively. This value increased to +59.1±11.4% of baseline on day 4 after CNO injection. Mean NREM bout duration averaged 1.4±0.2 min at baseline, 2.3±0.3 min on CSR day 1, 2.3±0.5 min on day 3 (vehicle), 3.5±0.4 min on day 4 (CNO) and 2.4±0.4 min on day 5 (vehicle).
Conclusion: All three indices of the homeostatic response to sleep loss increased following chemogenetic silencing of CRF neurons by CNO injection on day 4 CSR, compared to vehicle injections on CSR days 3 and 5. These findings support the hypothesis that activation of CRF neurons in the hypothalamic paraventricular nucleus (PVN) contributes to the attenuation of sleep homeostasis during CSR.

Disclosures: S. Kumar: None. **K. Hsieh:** None. **D. McGinty:** None. **R. Szymusiak:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.08/II12

Topic: F.04. Stress and the Brain

Support: Wellcome Trust

NIAAA IRP

Title: 5-HT neurons regulate fear learning by modulating basolateral amygdala circuits

Authors: *A. SENGUPTA[1,2], M. BOCCHIO[3,2], Z. A. MCELLIGOTT[4], T. KASH[4], M. CAPOGNA[5,2], D. M. BANNERMAN[2], T. SHARP[2], A. HOLMES[1]
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Abstract: The neurotransmitter serotonin (5-HT) is targeted by drugs (e.g. selective serotonin reuptake inhibitors) widely used to treat mood disorders such as anxiety and depression, but mechanisms of 5-HT involvement still remain unclear. Fear learning, which is important for avoiding environmental threats and crucial for survival, can become maladaptive in mood disorders. Dysfunctional neural fear circuits may contribute to emotional dysregulation in the etiology of such disorders. Lesion studies demonstrate intact 5-HT fibers in the amygdala are necessary for normal fear behavior. Basolateral amygdala (BLA) circuits are a locus of fear learning and receive dense 5-HT input from the dorsal raphe nucleus. To understand the involvement of 5-HT signaling and to optimize the efficacy of 5-HT-targeting drugs, characterizing the mechanisms of 5-HT modulation during fear behavior is essential. Here, we investigate the regulation of BLA circuits by 5-HT projections during fear learning. We virally delivered light-gated opsins, or a control inert protein, in mice to selectively control 5-HT inputs to the BLA. First, we manipulated 5-HT fiber activity during a fear learning task to establish the role of 5-HT projections to the BLA. We provide evidence for the bidirectional involvement of 5-HT by showing 5-HT fiber excitation or inhibition enhances or reduces conditioned fear behavior, respectively. We then conducted in vivo electrophysiology recordings that suggest 5-HT fiber excitation alters the responsiveness of the BLA to sensory stimuli during fear learning. To study the mechanisms of this modulation, we excited 5-HT fibers in ex vivo brain slices and recorded light-evoked postsynaptic potentials in BLA neurons that were abolished by 5-HT or glutamate receptor antagonists. Thus, we demonstrate the co-release of 5-HT and glutamate from 5-HT fibers in the amygdala. 5-HT and glutamate signals were targeted to distinct BLA cell types. Collectively, our study provides new insight into serotonergic mechanisms in amygdala function and in emotional behaviors that are aberrant in psychiatric illnesses. Specifically, we

find 5-HT inputs to the BLA modulate particular cell types through 5-HT and glutamate co-release, thereby regulating fear learning.

Disclosures: **A. Sengupta:** None. **M. Bocchio:** None. **Z.A. McElligott:** None. **T. Kash:** None. **M. Capogna:** None. **D.M. Bannerman:** None. **T. Sharp:** None. **A. Holmes:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.09/II13

Topic: F.04. Stress and the Brain

Support: NIH Grant MH048698

Title: Anxiolytic actions of glucocorticoid receptor knockdown in bed nucleus of the stria terminalis projecting neurons in the rat

Authors: *R. D. MOLONEY[1], J. R. SCHEIMANN[1], P. MAHBOD[1], B. A. PACKARD[1], R. L. MORANO[1], Y.-C. HU[2], J. P. HERMAN[1]
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Abstract: Aberrant glucocorticoid receptor (GR) signaling plays a role in numerous stress-related disorders related to anxiety and depression. Limbic regions of the brain such as the bed nucleus of the stria terminalis (BNST) are traditionally associated with affective behaviors. To understand the role of GR in BNST projections, we generated a conditional GR knockdown rat (Sprague-Dawley (SD) strain) using CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/ Cas 9 gene editing technology. Small guide (sg)RNAs were generated to target sequences 5' and 3' of exon 3 of the rat GR gene (nr3c1). Following sgRNA targeting, oligodeoxynucleotide donor sequences containing loxP sites were ligated into corresponding regions of the GR gene. Appropriate incorporation of loxP sites was verified by PCR, confirmed by DNA sequencing and further verified in vivo by AAV9-CaMKII-Cre-mediated deletion of GR in cortex. To specifically query the role of GR in limbic stress circuitry, we introduced a Canine adenovirus-Cre recombinase (Cav2-Cre) construct into the BNST region of female SD:nr3c1fl/fl or littermate wild type (SD:nr3c1wt/wt) rats. Cav2-Cre is retrogradely transported to the cell bodies of BNST-projecting neurons, affording circuit-specific deletion of the GR. Animals received bilateral injection of Cav2-Cre virus to the BNST and allowed to recover for 3 weeks prior to commencement of behavioral analysis. Animals underwent multiple behavioral assays to assess changes in anxiety- (open field, elevated plus maze (EPM)), depressive- (forced swim test (FST)), inhibitory/fear- (passive avoidance, fear conditioning) and cognitive- (novel object recognition (NOR)) behaviors. Our results indicate that knockdown of GR in BNST

projections increases open arm time and decreases closed arm entries in the EPM, increases exploratory behavior in the NOR task and increases saliency of the cue, as a predictor of the aversive stimulus during fear conditioning, but does not affect immobility in the FST. These data are consistent with the role of the BNST as an important relay for upstream limbic pathways regulating anxiety- and fear-related responses, and also demonstrate the utility of the conditional knockout rat model for assessment of GR action in a non-murine species.

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Poster

069. Stress-Modulated Pathways: Behavior and Cognition

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Program#/Poster#: 069.10/II14

Topic: F.04. Stress and the Brain

Support: R15MH104485

Title: Anxiolytic effects of orexin 2 receptors during stressful social interaction

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Abstract: Orexin 2 (Orx_2, hypocretin 2) receptor antagonism blocks the anxiolytic response of escape during stressful social aggression. Small adult test mice (C57Bl6NJ) were subjected to social aggression from a novel larger CD1 aggressor for 4 days in the Stress-Alternatives Model (SAM) arena. Prior to social interaction a tone was used as a conditioning stimulus (CS) that predicted removal of an opaque divider that allowed for social interaction. As in previous experiments, some individual test mice escaped social aggression through a portal only large enough for the smaller mouse, and others remained submissively. On day 3, icv injections of vehicle, Orx_2 agonist (Ala^{11}-D-Leu^{15}-Orx_B, 0.3 nmol), or Orx_2 antagonist (MK-1064, 0.3 nmol) were given prior to social interaction. The SAM apparatus is an oval open field arena with 2 escape routes on either end leading to a small safety area. It is employed for 5 min aggressive interactions, unless the animal escapes, in which case the interaction is shorter. Escape and latency to escape are direct measures of reduced anxiety. Submissive behavior is a reflection of heightened anxiety, and can be reversed by anxiolytic drugs or behaviors (e.g. exercise). Our previous research suggests that Orx_2 receptor activity in the basolateral amygdala (BLA) produces anxiolytic behavioral effects. This raises the question of whether the anxiolysis is strictly localized to BLA, or more generally attributable to the central nervous system.

Ventricular injection of Orx_2 antagonists inhibited escape behavior. In addition, icv Orx_2 antagonism increased freezing in response to Pavlovian conditioning as well as to aggressive social interaction. Startle responses were also significantly increased by inhibition of Orx_2 receptors during the social interaction. These results suggest that pervasive inhibition of Orx_2 receptors in the brain results in anxiogenic responses similar to those produced in the BLA. Systemic brain Orx_2 anxiolytic action suggests a potential for translational significance for affective disorders such as social anxiety and depression.

Disclosures: C.D. Staton: None. **J.D. Yaeger:** None. **F. Haroun:** None. **D.D. Khalid:** None. **T.C. Seidel:** None. **T.R. Summers:** None. **P.J. Ronan:** None. **C.H. Summers:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.11/II15

Topic: F.04. Stress and the Brain

Support: NIH Grant R15 MH107007

Title: Effects of social dominance on defeat-induced neural activity in a ventral hippocampus-to-basolateral amygdala circuit

Authors: *K. S. BRESS, B. N. DULKA, M. A. COOPER
Univ. of Tennessee, Knoxville, TN

Abstract: Interactions between the ventral hippocampus (vHPC) and the basolateral amygdala (BLA) play a critical role in the processing of emotional memories. While these brain regions are implicated in the development of stress-related mental illness, the role of a vHPC-to-BLA neural circuit in susceptibility to the effects of stress is not well understood. After exposure to acute social defeat stress, male Syrian hamsters exhibit increased submissive behavior and decreased territorial aggression in novel social encounters. This behavioral response is called conditioned defeat (CD). Importantly, hamsters with subordinate social status display an elevated CD response compared to dominants and controls. In this study, we hypothesized that subordinate hamsters would show increased neural activity following social defeat in a vHPC-to-BLA neural circuit compared to their dominant counterparts. Adult male Syrian hamsters were paired in daily agonistic encounters for 14 days, during which they formed stable dominance relationships. On day 9, stereotaxic surgery was performed and cholera toxin B (CTB) was injected unilaterally into the BLA. After a 48-hour recovery period, animals completed days 10-14 of their dominance interactions. Twenty-four hours after the last dominance encounter, dominant, subordinate, and social status control animals were exposed to acute social defeat stress, consisting of three 5-min defeats at 5-min intervals. Sixty minutes after the third defeat or empty

cage control experience, hamsters were transcardially perfused and brains were collected for CTB and c-Fos immunohistochemistry. We found that social defeat increased the number of c-Fos positive cells in the vHPC, but that dominance status did not significantly alter total c-Fos expression. We are currently quantifying the number of c-Fos/CTB double-labeled cells in the vHPC in dominants, subordinates, and controls. These results will address the cellular mechanisms that modulate status-dependent differences in susceptibility to acute social defeat and extend our understanding of the neural circuits that underlie the development of stress-related mental illness.

Disclosures: K.S. Bress: None. **B.N. Dulka:** None. **M.A. Cooper:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.12/II16

Topic: F.04. Stress and the Brain

Support: NARSAD Grant 19260

NeuroNET Seed Grant, UTK

Title: Short-term alcohol consumption alters stress susceptibility and BDNF activity in in a stressor-dependent and brain region-specific manner

Authors: A. GRIZZELL[1], J. LINDSAY[2], B. N. DULKA[3], *R. A. PROSSER[2], M. A. COOPER[3]
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Abstract: The relationship between alcohol use and stress reactivity is complex. Depending on the context, alcohol may dampen or enhance the stress-induced affective states. Research shows that many factors can mediate this discrepancy, for instance the timing of consumption relative to stress experience, duration of either alcohol and stress exposure, and modalities of stress and alcohol administration. Despite this, little is known regarding the mechanisms by which alcohol consumption alters responses to acute stress. Here, we demonstrate that alcohol self-administration (15%, 4-hr drinking-in-dark paradigm) for 1 week before and immediately following acute stress exposure in adult male C57Bl/6 mice interacts in a stressor and brain region-dependent manner to alter social avoidance. Mice were exposed either to an acute social defeat procedure (2-min encounters with 3 resident CD1 mice at 2-min intervals) or to an acute variable stress (AVS) procedure consisting of acute restraint (20 mins) followed immediately by social defeat (as above) and forced swim (20 mins). In water drinking mice, there was a main

effect of stress wherein both social defeat alone and AVS elevated social avoidance compared to non-stressed mice. However, alcohol exposure exacerbated social avoidance in mice exposed to social defeat alone while it normalized social avoidance in AVS mice to control levels. Because BDNF activity has been shown to regulate the effects of chronic social defeat and conditioned fear in the nucleus accumbens shell and amygdala (BLA/CeA) respectively, we investigated the expression of pro and m(ature) BDNF as well as TrkB receptors in these regions via Western blot assays. Preliminary data suggest that in the accumbens of alcohol exposed mice, social defeat alone induces an upregulation of mBDNF while AVS induces no change 24 hrs after stress. Furthermore, alcohol and social defeat stress (but not AVS) interact to increase TrkB expression in the accumbens. In the amygdala, AVS (but not social defeat) elicits an upregulation of pro and mBDNF following alcohol exposure only in mice that are susceptible to stress induced social avoidance. Taken together, our results suggest that short term alcohol exposure prior to and after stress interacts in a stressor and brain region specific manner to alter behavior in mice susceptible to acute stress. The differential effects appear to involve an alcohol-dependent and stressor-specific upregulation of BDNF activity in the accumbens in exclusively social conditions and in the amygdala in variable stress conditions.

Disclosures: A. Grizzell: None. **J. Lindsay:** None. **B.N. Dulka:** None. **R.A. Prosser:** None. **M.A. Cooper:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.13/II17

Topic: F.04. Stress and the Brain

Support: NIH Grant MH107007

Title: Dominance relationships in Syrian hamsters modulate defeat-induced neural activity in an infralimbic cortex-to-basolateral amygdala circuit

Authors: *B. N. DULKA, K. S. BRESS, M. A. COOPER
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Abstract: Stress is a contributing factor in the etiology of several mood and anxiety disorders, and animal models of social defeat stress have been increasingly used to investigate the biological basis of stress-related psychopathologies. Male Syrian hamsters are highly aggressive and territorial, but after a defeat experience they exhibit a conditioned defeat (CD) response which is characterized by increased submissive behavior and a failure to defend their home territory against a smaller, non-aggressive intruder. Hamsters that achieve dominant social status show increased c-Fos expression in the infralimbic (IL) cortex following social defeat and

display a reduced CD response at testing compared to subordinates and controls. Pharmacological inactivation of the ventromedial prefrontal cortex (vmPFC) prevents resistance to CD in dominants without affecting CD in subordinates or controls, suggesting that neural activity in the vmPFC is necessary for CD resistance. In this study, we tested the hypothesis that dominant hamsters would show increased defeat-induced neural activity in IL neurons that send efferent projections to the basolateral amygdala (BLA) compared to their subordinate counterparts. We paired male Syrian hamsters in daily dominance encounters for 14 days, during which they formed stable dominance relationships. After the 9th day of dominance encounters, animals underwent stereotaxic surgery and cholera toxin B (CTB) was injected unilaterally into the BLA. Dominance encounters resumed 48 hours later for days 10-14 of social interactions. Then, 24 hours after the last dominance encounter, dominant, subordinate, and social status control hamsters received acute social defeat, which consisted of three 5-min social defeat episodes at 5-min intervals. Sixty minutes after social defeat stress or no defeat control procedures, animals were euthanized and brains collected for CTB and c-Fos dual immunohistochemistry. Preliminary results suggest that dominant hamsters have a greater number of double-labeled c-Fos/CTB immuno-positive cells in the IL compared to subordinates. These findings suggest that dominant hamsters selectively active an IL-to-BLA neural circuit following social defeat, which may be responsible for their reduced CD response. This project extends our understanding of the neural circuits underlying stress resistance which is an important step towards identifying novel targets for the prevention and treatment of stress-related psychopathology.

Disclosures: B.N. Dulka: None. **K.S. Bress:** None. **M.A. Cooper:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.14/II18

Topic: F.04. Stress and the Brain

Support: NeuroNET Seed Grant, UTK

Title: Cotinine confers a proactive coping strategy during and normalizes anxiety following acute social defeat

Authors: *A. GRIZZELL[1], J. H. LINDSAY[2], H. JANG[1], R. A. PROSSER[2], V. ECHEVERRIA[3], M. A. COOPER[1]
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Abstract: Elevated tobacco use is often reported in patients with stress-related psychopathologies and coincides with a self-reported reduction of symptoms which suggests that components of tobacco have stress relieving properties. While the effects of nicotine on stress-induced affective states are equivocal, research on cotinine, the primary metabolite of nicotine, suggests that it has distinct effects on behavior and brain function. Cotinine reduces chronic stress-related memory and mood impairment, facilitates the extinction of conditioned fear, and attenuates acute stress-induced anxiety-like behavior. Furthermore, cotinine confers a proactive coping strategy in a forced swim test. In this study, we tested whether repeated cotinine treatment would reduce the effects of acute social defeat stress in male C57Bl/6 mice. We found that 7 days of oral cotinine treatment (5 mg/kg) significantly reduced time mice spent exhibiting submissive and defensive postures during social defeat encounters despite receiving similar levels of aggression. During periods when the CD1 aggressor was not attacking the subject, cotinine-treated mice displayed less time exhibiting fear-related behaviors such as freezing, fleeing, avoiding, and defensive monitoring compared to vehicle-treated mice. In a subset of mice (30%), cotinine promoted defensive aggression which at times even resulted in defeating the resident CD1 aggressor. Interestingly, this occurred despite each mouse having first displayed submissive behavior, which is unprecedented in social defeat models. To determine if cotinine's effects during the defeats were due to a general enhancement of aggression, agonistic behavior was monitored immediately upon reintroduction to their cagemate. Whereas 60% of vehicle-treated mice were observed briefly fighting upon return to their home cage, none of cotinine-treated mice displayed aggressive behavior toward their original cage mates. Twenty-four hours later, a social interaction test was used to assay social defeat-induced social avoidance followed by anxiety-like behavior in a light/dark (LD) transition test. There was a main effect of stress wherein social defeat significantly increased social avoidance, but no significant effects of cotinine were observed. However, cotinine normalized the stress-induced change in anxiety-like behavior in the LD test. Taken together, our results extend previous findings that cotinine confers a proactive coping strategy during stress exposure and normalizes stress-induced anxiety-like behavior. Furthermore, these effects are not likely due to an enhancement of aggression or an impairment of emotional memory.

Disclosures: A. Grizzell: None. **J.H. Lindsay:** None. **H. Jang:** None. **R.A. Prosser:** None. **V. Echeverria:** None. **M.A. Cooper:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.15/II19

Topic: F.04. Stress and the Brain

Support: NIH Grant R15 MH107007

Title: Sex differences in the effects of social status on defeat-induced social avoidance in Syrian hamsters

Authors: A. L. LOEWEN, A. V. CAMPBELL, B. N. DULKA, J. A. GRIZZELL, *M. A. COOPER
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Abstract: Understanding the neuroendocrine mechanisms that support stress resilience is an early step toward developing more effective treatment options for patients who suffer from stress-related psychopathologies. Although social defeat models in male rodents are frequently used to investigate the cellular mechanisms of stress susceptibility, much less research has included females. We have previously shown that male Syrian hamsters exhibit elevated social avoidance following acute social defeat stress. Interestingly, male hamsters with dominant social status exhibit elevated plasma testosterone, increased androgen receptor expression in the medial amygdala (MeA) and ventral lateral septum (vLS), and less defeat-induced social avoidance compared to subordinates and controls. The objective of this study was to investigate whether dominant female hamsters show changes in testosterone concentration, androgen receptor expression, and defeat-induced social avoidance. Adult female hamsters were matched according to their estrous cycle and paired in 12 daily social encounters to establish dominance relationships. To avoid dyadic encounters when females were in estrous, we skipped encounters every 4 days. Male hamsters were similarly paired in dominant/subordinate dyads for 12 days. Blood was collected from both male and female subjects prior to and 15 min following their first dominance encounter. After the final dominance encounter, animals experienced acute social defeat stress and 24 hours later received a social interaction test with a same-sex, unfamiliar, confined hamster. While acute social defeat stress produced social avoidance in both male and female hamsters, social status altered social avoidance and plasma testosterone in males but not females. Whether social status alters the expression of androgen and estrogen receptors in the MeA and vLS will also be addressed. These findings suggest the neuroendocrine mechanisms controlling the effects of social status on defeat-induced changes in behavior in male hamsters do not generalize to female hamsters. This line of research improves our understanding of the neuroendocrine mechanisms regulating sex differences in vulnerability to stress-related mental illness.

Disclosures: A.L. Loewen: None. **A.V. Campbell:** None. **B.N. Dulka:** None. **J.A. Grizzell:** None. **M.A. Cooper:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: F.04. Stress and the Brain

Support: NINDS T32-NS007431

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NICHD T32-HD079124

NIMH T32-MH093315

Title: Encoding the relationship between anxiety-related behaviors and nociceptin neurons of the bed nucleus of the stria terminalis

Authors: *R. L. UNG[1], J. RODRIGUEZ-ROMAGUERA[1], H. NOMURA[1], V. M. K. NAMBOODIRI[1], J. M. OTIS[1], J. ROBINSON[1], S. L. RESENDEZ[1], J. A. MCHENRY[1], L. E. H. ECKMAN[1], O. KOSYK[1], H. E. VAN DEN MUNKHOF[1], P. ZHOU[3], L. PANINSKI[3], T. KASH[2], M. R. BRUCHAS[4], G. D. STUBER[1]
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Abstract: Anxiety is a complex emotional state characterized by distinct behaviors and diverse neuronal subtypes that span multiple brain regions. The bed nucleus of the stria terminalis (BNST) is one region that is critical in governing these anxiety-related behaviors, and the genetic diversity of its neuronal population is likely an important component in modulating the vast behaviors expressed during anxiety states. However, this genetic heterogeneity also makes understanding this relationship difficult. Cre driver lines are powerful tools that can address this challenge, and in this study, we utilize a novel Cre drive line to study the role of BNST neurons that express prepronociceptin ($BNST^{PNOC}$): a precursor protein implicated in processes such as pain and anxiety. We use *in vivo* calcium imaging in freely behaving PNOC-Cre mice to determine the neural dynamics of this population in anterodorsal BNST during anxiety states. Globally, these neurons increase activity in epochs where mice are in the open arms of the elevated plus maze (EPM) when compared to epochs in the closed arm. Considering behaviors are far more complex than location within EPM, we measured additional anxiety-related behaviors expressed during the EPM assay (e.g., transitions between arms, distance from edge of open arm, velocity, and freezing) to model the neural dynamics of individual neurons as a function of these behaviors. Using multiple linear regression, we use a combination of behavioral variables to define neural activity of each neuron and find that distinct subsets of neurons have different relationships between its activity and expression of anxiety-related behaviors. For example, distance from the edge of open arms and velocity are significant predictors of neural activity in a subset of $BNST^{PNOC}$ neurons. In order to determine these effects are not specific to

the EPM, we examine the relationship between $BNST^{PNOC}$ and anxiety-related behaviors in mice exposed to predatory odor (2,3,5-trimethyl-3-thiazoline [TMT]) within their homecages. Similarly, we find that both distance to TMT and velocity are significant explanatory variables of neural activity for a subset of $BNST^{PNOC}$ neurons. Importantly, many neurons fail to convey this relationship when the odor is neutral (water) or rewarding (peanut oil). These findings suggest that $BNST^{PNOC}$ neurons may be an important population in guiding anxiety-relevant behaviors and, consequently, a potential target for future therapeutics.

Disclosures: R.L. Ung: None. **J. Rodriguez-Romaguera:** None. **H. Nomura:** None. **V.M.K. Namboodiri:** None. **J.M. Otis:** None. **J. Robinson:** None. **S.L. Resendez:** None. **J.A. McHenry:** None. **L.E.H. Eckman:** None. **O. Kosyk:** None. **H.E. van den Munkhof:** None. **P. Zhou:** None. **L. Paninski:** None. **T. Kash:** None. **M.R. Bruchas:** None. **G.D. Stuber:** None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.17/II21

Topic: F.04. Stress and the Brain

Support: R01MH105528

Title: Persistent pain intensifies the recall of consolidated fear memories

Authors: *E. DIMITROV
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Abstract: The deleterious impact of chronic pain on learning, memory and mood is well documented. Long-lasting pain leads to anxiety, depression and negatively affects the formation of new memories. We hypothesized that chronic pain may affect even memories that were established before the onset of pain. Mice underwent a classic auditory fear conditioning with 30 seconds 75 dB tone as a conditioned stimulus (CS) paired with 2 seconds 1 mA electric foot shock as unconditioned stimulus (US). Sciatic nerve constriction was used to induce neuropathic pain 48 hours after the fear conditioning. The nerve constriction reliably produced mechanical allodynia that lasted for the duration of the experiments. Two sessions of fear recall were conducted 14 days and 28 days after the initiation of neuropathic pain. Mice with neuropathic pain showed an increased percent of time freezing to CS (t_{36} =3.9, P<0.001). The cuffed mice once again spent more time freezing when tested 28 days after the beginning of pain (t_{36}= 4.8, P< 0.001). Next, the mice were pretreated with analgesic dose of NSAID before the fear recall. However, analgesia did not change the increased freezing time in neuropathic mice neither at 14 or 28 days after the sciatic nerve constriction.
Long-lasting neuropathic pain also induced changes in the parvalbumin interneurons of

basolateral amygdala (BLA). The number of immunopositive parvalbumin neurons increased in mice with neuropathic pain ($t_{23} = 4.3$, $P < 0.001$) and most of these parvalbumin neurons did not have perineuronal nets ($t_{19} = 4.6$, $P < 0.01$). Finally, the mice where tested for anxiety and depression. The experimental group did not display any increased anxiety- or depression-like behavior in comparison to the control groups neither at 14 or 28 days after the nerve constriction. This is consistent with the time frame for developing anxiety- and depression-like behavior already described in the literature.
In conclusion, our studies provide evidence for the impact of persistent pain on already consolidated fear memories. Very likely the underlying mechanism for this phenomenon is increased inhibitory tone of parvalbumin neurons onto other types of inhibitory interneurons in the amygdala, which may result in overall disinhibition of the pyramidal neurons. It is possible that the increased fear recall to already consolidated fear memory is a harbinger for the later development of anxiety and depression symptoms associated with chronic pain.

Disclosures: E. Dimitrov: None.

Poster

069. Stress-Modulated Pathways: Behavior and Cognition

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 069.18/II22

Topic: F.04. Stress and the Brain

Support: CAPES

CNPQ

FAPEMIG

UFOP

Title: High-fat diet effects on behavioral, neuronal activity, central inflammation and cutaneous temperature in male Wistar rats subjected to behavioral paradigms

Authors: *S. I. NORONHA, G. S. V. CAMPOS, P. M. A. LIMA, A. B. FIGUEIREDO, L. C. C. AFONSO, D. A. CHIANCA-JR, R. C. A. MENEZES
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Abstract: Background - Chronic high fat diet (HFD) consumption leads to autonomic impairment by increasing blood pressure and heart rate and has been associated as a cause for anxiety-like vulnerability in rats. Fear responses caused by several stressors paradigm has been largely use to investigate behavioral assessment. In this sense, our aim was to investigate the neuronal activation and the neuroinflammation responses in the hypothalamus and the amygdala

of HFD subjects exposed to the Elevated T-maze. We also investigated the autonomic activity of these animals by assessing the tail skin and the interscapulum cutaneous temperature along the Open Field test. **Methods** - using the model of obesity-induced by a 9 weeks high fat diet (HFD), compared to a normal diet (ND) model, we investigated rats behavioral using the Elevated Plus Maze (EPM), Elevated T-maze (ETM), light/dark box (LD) and the Open Field arena (OF). Neuronal activity by the immediate early gene cfos changes during handling, avoidance or escape task (ETM), in the hypothalamus (DMH, VMH and PVN) and the basolateral amygdala (BLA). Inflammatory response by measurement of IL1-β, TNFα and IL-6 in the same nuclei as above. Interscapulum cutaneous temperature (ICT) and tail skin temperature (TST) during OF test. **Results** - Behavioral assessment revealed that HFD animals have exacerbated avoidance behavior compared to ND animals when tested in the EPM and ETM, but showed no difference when tested in the LF and OF test. Immediate early gene cfos was higher in HFD group during avoidance task in the ETM comparing to the ND, in the DMH, VMH and the BLA. In the other hand, for escape task we found an increase for both ND and HFD in the BLA and VMH comparing to handling animals, and a higher activation in the DMH and PVN of ND animals compared to HDF animals. Using Elisa immunoassay, we could not detect the IL-1β values in the hypothalamus and amygdala. For IL-6 and TNFα we detected differences between HFD and ND in the BLA, and in IL-6 in the hypothalamus. ICT was higher in both ND and HFD comparing to baseline, and HFD ICT temperature was higher in time point 2 (begin of OF stress) and time point 15 (begin of resting). TST increased in HFD and ND along the stress and recovery periods. Importantly, the TST was higher in HFD group during the stress and recovery periods. **Conclusions** - Our results confirms that HFD-animals present anxiety-like behaviors and increased autonomic activity. More importantly our results show an increased neuronal activation during the avoidance test, within brain regions involved in controlling anxiety-like behaviors, possible caused by the neuroinflammation in these regions.

Disclosures: S.I. Noronha: None. **G.S.V. Campos:** None. **P.M.A. Lima:** None. **A.B. Figueiredo:** None. **L.C.C. Afonso:** None. **D.A. Chianca-Jr:** None. **R.C.A. Menezes:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.01/II23

Topic: F.04. Stress and the Brain

Support: University of Delaware Support Grant

Title: Differential gene expression induced by intranasal and subcutaneous routes of oxytocin administration in rats

Authors: *T. CHAKRABORTY[1], J. SCHULKIN[2], J. B. ROSEN[3]
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Abstract: Oxytocin (OT), a peptide hormone, delivered by intranasal or systemic routes affects learning and memory, fear and anxiety, and social interaction in humans and animals. Clinical trials suggest that intranasally-delivered oxytocin can ameliorate symptoms of schizophrenia, autism, and post-traumatic stress syndrome. These studies use changes in brain activity in imaging experiments and cerebrospinal fluid OT concentration as evidence that OT penetrates the blood brain barrier to influence behavior and brain activity. However, the dose-response relationship of exogenous OT on neuronal activity from intranasal and systemic routes is not known. Our goals are first to estimate the plasma concentration needed for OT to cross the blood brain barrier (BBB) using an *in vitro* model of the BBB. Second, we aim to determine intranasal and subcutaneous doses of exogenous OT that influence neural activation by measuring expression of immediate-early genes in the brain. An artificial *in vitro* BBB system was used to determine the concentration of OT in the "blood side" needed for OT to penetrate the artificial BBB. In our system, at least 100 ng/ml of exogenous OT in the luminal "blood side" fluid was needed to penetrate the BBB and significantly accumulate on the abluminal "brain side" compared to no exogenous OT. Male Sprague-Dawley rats were administered various doses of OT either intranasally or subcutaneously. 30 min after OT was administered, trunk blood and brain were collected. An ELISA assay found that subcutaneous doses of 10 µg and 1 mg per kg increased blood plasma OT sufficiently to indicate OT would cross the BBB. Intranasal doses up 20 µg did not reach sufficient plasma levels to suggest OT would cross the BBB. *In situ* hybridization of *Egr-1* demonstrated decreased and increased expression in the PVN with intranasal (20 µg) and subcutaneous (1 mg/kg) OT, respectively. In addition, 1 mg/kg subcutaneous OT induced *Egr-1* exrpession in the central nucleus of the amygdala, whereas a lower dose of 0.1 µg/kg OT significantly increased *Egr-1* expression in the CA3 of the hippocampus. The data suggest that route of administration and dose influence how exogenous OT affects brain activity. Studies examining other immediate-early genes (e.g., *C-fos)* will be performed to develop a broader picture of the effects of exogenous OT via different routes of administration on brain activity important of inferring clinical effects of OT.

Disclosures: T. Chakraborty: None. **J. Schulkin:** None. **J.B. Rosen:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.02/II24

Topic: F.04. Stress and the Brain

Support: NIH Grant DA042475

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NIH Grant DA034428

Title: Uncovering the excitatory roles of postsynaptic alpha$_{2A}$-adrenergic receptors within the bed nucleus of the stria terminalis

Authors: *N. A. HARRIS[1,2,3,4,5], A. T. ISAAC[2,3], M. A. XU[2,3], S. A. FLAVIN[4,6], R. GILSBACH[7], L. HEIN[7], D. G. WINDER[2,3,4,5,6]
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Abstract: Stress is a major risk factor for relapse to drug-seeking behavior. Guanfacine, an α2A-adrenergic receptor (AR) agonist, decreases stress-induced craving in humans. In rodents, systemic or intra-BNST injections of α2-AR agonists reduce stress-induced reinstatement behaviors. We have shown presynaptic inhibitory effects of guanfacine on excitatory drive in the BNST. In contrast, guanfacine both enhances optically evoked BNST field potentials in a Thy1-COP4 transgenic mouse line and induces cfos expression in BNST neurons. Here we investigate the mechanisms underlying the non-canonical activity-enhancing effects of guanfacine. We find that guanfacine-induced cfos expression is not present in full α2A-AR knockout mice and NONadrenergic-specific α2A-AR knockout mice, suggesting a heteroceptor-mediated mechanism. Second, using a cfos-eGFP mouse line, we show that preincubation of *ex vivo* BNST slices in 1 uM guanfacine is sufficient for atipamezole-sensitive cfos expression, suggesting sufficiency of local BNST α2A-ARs for cfos expression. Further consistent with this idea, we find that cfos upregulation occurs in BNST predominantly in adra2a+ (α2A-AR) BNST neurons. To test the sufficiency of postsynaptic G_i-coupled GPCR signaling in cfos induction, we assessed the ability of clozapine-N-oxide (CNO) to induce fos in BNST in mice in which hM4Di was expressed in the BNST. We found that systemic CNO, guanfacine, or CNO+guanfacine yielded similar increases in BNST cfos expression. These complementary results suggest that postsynaptic α2A-ARs mediate guanfacine-induced cfos expression in the BNST. We hypothesized that this occurs via decreased cAMP-dependent opening of hyperpolarization-activated cyclic nucleotide-gated nonselective cation (HCN) channels. Here we show that guanfacine-activated neurons identified as cfos-eGFP+ express I_h and that a majority of adra2a+ BNST neurons co-localize with hcn2 but not hcn1 transcripts, suggesting the potential for interaction. In addition, HCN channel inhibition by ZD7288 is sufficient for enhancement of optical field potentials in the Thy1COP4 transgenic mouse line. In total these data suggest novel excitatory actions of α2-ARs in BNST.

Disclosures: **N.A. Harris:** None. **A.T. Isaac:** None. **M.A. Xu:** None. **S.A. Flavin:** None. **R. Gilsbach:** None. **L. Hein:** None. **D.G. Winder:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.03/II25

Topic: F.04. Stress and the Brain

Title: Estrogen influences hypothalamic-pituitary-axis activation in female rats following acute restraint in the presence of sodium deficiency

Authors: *C. RAYMOND, K. S. CURTIS
Pharmacology/Physiology, Oklahoma State Univ. Ctr. For Hlth. Scienc, Tulsa, OK

Abstract: Hypothalamic-pituitary-adrenal (HPA) axis activation and the subsequent release of stress hormones into circulation is essential in responses to stressors. Glucocorticoids also play an integral role in the adaptation to stress through negative feedback to the HPA axis. Stressors, both physiological and psychogenic, are associated with deviations from homeostasis, and therefore the adaptive role of the HPA axis and glucocorticoids are important in restoring homeostasis. Physical restraint is a psychogenic stressor that is often used in animal studies of stress responses to activate the HPA axis and cause the release of glucocorticoids from the adrenal cortex. In addition to psychogenic stress, physiological challenges such as prolonged sodium imbalance also serve as stressors. Although human stress disorders are more prevalent in females, animal studies are typically conducted in males. At present, there is limited knowledge regarding the role of estrogen in HPA axis activation and feedback to restore homeostasis following physiologic stressors in female rats. Moreover, it is unknown whether estrogen influences interactions between psychogenic and physiologic stressors. This study investigated the effect of estrogen on corticosterone levels following acute restraint in the presence of sodium deficiency in ovariectomized female rats. All procedures were approved by the Oklahoma State University - Center for Health Sciences Animal Care and Use Committee. Female Sprague-Dawley rats were anesthetized with pentobarbital and ovariectomized, then allowed one week of recovery before initiation of a 10-day experimental protocol during which they were maintained on sodium deficient (Na-D) or control regular sodium (Na-R) diet. Rats were given subcutaneous injections of estradiol benzoate (EB) suspended in sesame oil or control injections of sesame oil (OIL) on days 1-2 and 7-8, to mimic fluctuations during the 4-day estrous cycle of female rodents, and to isolate the effects of estrogen. On day 10, half the rats in each condition were placed in a clear plexiglass apparatus for 15 minutes, which served as the acute psychogenic stressor; the remainder of the rats were not restrained. As expected, plasma corticosterone, measured by Elisa kit, was increased by acute restraint, and this response was enhanced by estrogen. In contrast, estrogen blunted the plasma corticosterone response when acute restraint occurred after 10 days of dietary sodium deficiency. These results suggest that estrogen alters

glucocorticoid responses to a combination of prolonged physiologic and acute psychogenic stressors, which may influence the ability to restore homeostasis.

Disclosures: C. Raymond: None. **K.S. Curtis:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.04/II26

Topic: F.04. Stress and the Brain

Support: CIHR

NSERC

Ontario Mental Health Foundation

Title: Loss of cAMP-dependent synaptic potentiation during habituation to repeated stress

Authors: *J. K. SUNSTRUM[1], E. W. SALTER[1], W. INOUE[1,2]
[1]Neurosci., [2]Robarts Res. Inst., Univ. of Western Ontario, London, ON, Canada

Abstract: The activation of the hypothalamic-pituitary-adrenal (HPA) axis—the neuroendocrine stress response—relies on the release of corticotropin releasing hormone (CRH) from neuroendocrine neurons in the paraventricular nucleus of the hypothalamus (PVN). The stress-induced activation of these PVN-CRH neurons is in part driven by neuromodulators, many of which act through cAMP. By using patch clamp electrophysiology in *ex vivo* brain slices prepared from CRH reporter mice, here we report that forskolin (an activator of cAMP signaling) increases both frequency and amplitude of spontaneous excitatory postsynaptic currents (sEPSCs) in PVN-CRH neurons. Moreover, this cAMP-induced increase in sEPSC amplitude but not frequency is attenuated following habituation to a repeated stressor (restraint stress). When forskolin-induced synaptic potentiation was further investigated in naïve mice, we found that inhibitors for hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (a target for cAMP) specifically prevented the forskolin-induced increase in sEPSC amplitude but not frequency. In contrast, inhibiting other pathways downstream of cAMP, such as protein kinase A (PKA), exchange protein directly activated by cAMP (EPAC) or extracellular-signal regulated kinase (ERK), did not prevent forskolin-induced sEPSC potentiation. This result indicates that the attenuation of cAMP-mediated synaptic transmission is a possible mechanism for stress habituation, and suggests a novel role for HCN channels in PVN-CRH synaptic transmission.

Disclosures: J.K. Sunstrum: None. **E.W. Salter:** None. **W. Inoue:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.05/II27

Topic: F.04. Stress and the Brain

Support: CIHR

NSERC

Ontario Mental Health Foundation

Title: Corticotropin releasing hormone neurons in the paraventricular nucleus of the hypothalamus decrease intrinsic excitability during habituation to repeated stress

Authors: *W. INOUE[1], S. MATOVIC[2], E. W. SALTER[2]
[2]Neurosci., [1]Univ. of Western Ontario, London, ON, Canada

Abstract: Habituating to repetitive yet non-life threating stressors is instrumental for minimising negative consequences of chronic stress. Here, we report a neuronal correlate for habituation of the hypothalamic-pituitary-adrenal (HPA) axis to repeated stress that manifest as a decrease in the excitability of HPA axis output neurons [neuroendocrine neurons that express corticotropin releasing hormone (CRH) in the paraventricular nucleus of the hypothalamus (PVN)]. We obtained whole cell patch clamp recordings from PVN-CRH neurons in slices from CRH reporter mice subjected to daily 1-h restraint stress up to 21 days. We found that 21-day stress caused two mechanistically dissociable changes: 1) it delayed the time to elicit an action potential in response to depolarizing current injections, 2) it decreased the frequency of repetitive firing during long-duration current injections. Interestingly, the spike delay developed quickly and became evident as early as after 1 and 7 day(s) of stress, and was reversed by 4-aminopyridine (4-AP), an A-type potassium channel blocker. By contrast, the decrease of spike frequency only became evident after 21 days of stress, and was not reversed by 4-AP. The spike frequency decrease was negatively correlated with a stress-induced increase in cell capacitance and whole-cell membrane conductance but not with unit membrane conductance. This points to stress-induced structural plasticity of PVH-CRH neurons controlling their intrinsic excitability, and hence cellular habituation during chronic stress.

Disclosures: W. Inoue: None. **S. Matovic:** None. **E.W. Salter:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.06/JJ1

Topic: F.04. Stress and the Brain

Support: Dept. Psychology & Neuroscience, Baylor University

Title: Gender differences in basolateral amygdala excitability following single-prolonged stress

Authors: *N. B. KEELE, L. C. ORNELAS, M. L. MCREYNOLDS
Baylor Univ. Dept. of Psychology and Neurosci., Waco, TX

Abstract: Individual responses to the negative consequences of stress vary, and the biological stress response differs in males and females. Uncovering gender differences in membrane properties of amygdala neurons from stressed animals may reveal potential neural mechanisms associated with resilience or susceptibility to stress. Using a well-established animal model of post-traumatic stress disorder (PTSD) called the single-prolonged stress (SPS) model, we tested the hypothesis that stress affects amygdala membrane excitability differently in males than in females. Animals were randomly assigned to one of four groups in a 2x2 (gender x stress) design. Both male and female rats in the SPS group were subjected to 2-hour whole body restraint, followed immediately by a 20 min forced swim test, then a 15 min recuperation period and lastly, ether-induced loss of consciousness. Animals in the unstressed control (USC) group were left undisturbed in their home cage, except for usual husbandry. Whole-cell recordings were obtained eight to 11 days after SPS, or the corresponding time for USC. Recordings were performed in brain slices containing the basolateral amygdala (BLA) from both male and female rats (approx. one to two months old) to determine SPS-induced changes in passive and active membrane properties in BLA neurons.

SPS altered membrane properties of BLA neurons selectively from female rats. In BLA neurons from females, resting membrane potential (RMP) was hyperpolarized following SPS compared to USC (USC -57.4 ± 4.7 mV, SPS -68.5 ± 0.2 mV; $t(13)=2.32$, $P<0.05$). However, SPS did not change RMP in BLA neurons from males (USC -59.6 ± 2.1 mV, SPS -61.6 ± 4.6 mV). Membrane excitability was examined further by measuring the first interspike interval (ISI) following a depolarizing current step (400 pA, 600 ms). The first ISI in BLA neurons from male rats was not different in cells from both SPS or USC groups (USC 16.5 ± 3.8 ms, SPS 26.5 ± 7.5 ms). The first ISI was significantly longer in BLA neurons in females exposed to SPS (USC: 21.1 ± 6.7 ms; SPS 84.3 ± 38.1 ms; $t(12)=2.9$, $P<0.05$).

Collectively, these data show there are gender differences in amygdala physiology following exposure to traumatic stress. Specifically, SPS hyperpolarized BLA neurons and decreased BLA

neuronal excitability only in females. Together, these data may have important implications in the physiological mechanism contributing to gender differences in anxiety disorders, specifically PTSD.

Disclosures: **N.B. Keele:** None. **L.C. Ornelas:** None. **M.L. McReynolds:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.07/JJ2

Topic: F.04. Stress and the Brain

Support: Department of Psychology and Neuroscience, Baylor University

Title: Single prolonged stress and ethanol contribute to basolateral amygdala excitability differently in males and females

Authors: *L. C. ORNELAS, M. L. MCREYNOLDS, N. B. KEELE
Psychology and Neurosci., Baylor Univ., Waco, TX

Abstract: Determining the neurophysiological effects of acute ethanol (EtOH) on basolateral amygdala (BLA) neurons in both males and females may lead to more effective treatment strategies of anxiety disorders such as post-traumatic stress disorder (PTSD), where alcohol use disorders are highly comorbid. While the effect of EtOH on anxiety and the amygdala is well-established, gender differences in the effects of EtOH on BLA neurophysiology and the effect of traumatic stress on EtOH-induced changes to BLA activity are currently unknown. This project uses an established animal model of PTSD, the single prolonged stress (SPS) model, to determine the interacting contributions of gender and traumatic stress on EtOH-induced changes of BLA excitability. Both male and female rats in the SPS group were subjected to 2-hour whole body restraint, followed immediately by a 20 min forced swim test, then a 15 min recuperation period and lastly, ether-induced loss of consciousness. Animals in the unstressed control (USC) group were left undisturbed in their home cage, except for usual husbandry. Whole-cell recordings were obtained eight to 11 days after SPS, or the corresponding age for USC. Recordings were performed in brain slices containing the BLA from both male and female rats (approx. one to two months old) to determine the effect of EtOH on membrane properties of BLA neurons from male and female rats exposed to SPS. Ethanol (30 mM) depolarized BLA neurons from both male and female rats subjected to SPS. EtOH (30 mM) elicited a depolarization of approximately 5 mV in BLA neurons from the SPS group (pre-EtOH: -69.2 ± 0.9 mV, EtOH: -64.3 ± 1.7 mV). EtOH had no effect on membrane potential of BLA neurons from USC (pre-EtOH: -58.1 ± 3.3 mV, EtOH: -55 ± 2.8 mV). Membrane excitability was

examined further by measuring the first interspike interval (ISI) following a depolarizing current step (400 pA, 600 ms). EtOH did not change ISI in BLA neurons from males in either USC or SPS groups. In BLA neurons from female rats, EtOH increased the first ISI in USC (pre-EtOH: 9.4 ± 1.4 ms, EtOH: 38 ± 14.8 ms). After SPS, BLA excitability was decreased in females, but excitability was not further decreased by EtOH (first ISI pre-EtOH: 157 ms, EtOH: 168 ms). Collectively, these data show that the EtOH decreases amygdala excitability in female rats more strongly than in males, and suggests SPS may further occlude EtOH-induced inhibition. These gender differences in responses to EtOH may have important implications in the physiological mechanisms contributing to anxiety disorders and alcohol abuse.

Disclosures: L.C. Ornelas: None. **M.L. McReynolds:** None. **N.B. Keele:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.08/JJ3

Topic: F.04. Stress and the Brain

Support: Dept. of Psychology & Neuroscience, Baylor University

Title: Adult and early life stress impair extinction learning and memory, and change GluA1 and PSD-95 expression in the infralimbic cortex but not the prelimbic cortex or amygdala

Authors: *M. L. MCREYNOLDS, L. C. ORNELAS, N. B. KEELE
Baylor Univ., Waco, TX

Abstract: Stress alters the structure and function of brain areas critical for fear learning and extinction, such as the amygdala and medial prefrontal cortex (mPFC), increasing the risk of developing psychiatric disorders. The effects of stress vary among brain regions, and are dependent on the duration, developmental timing, and type of stressor. Therefore, the aim of this project is to elucidate molecular mechanisms underlying stress-related deficits in fear behavior following early life and adult stress. Male Sprague-Dawley rats were subjected to maternal separation (2hr/day/PD 2-9, or unstressed control) or an acute adult stressor (15 min forced swim, or no swim control) in a 2x2 between groups design. Fear behavior was measured using a fear-potentiated startle paradigm and standard immunoblotting techniques were performed to determine stress-related changes in PSD-95 and AMPA glutamate receptor 1 (GluA1) expression in the basolateral amygdala (BLA), prelimbic cortex (PL), and infralimbic cortex (IL).
Neither early life stress (ELS), adult stress (AS), nor ELS followed by AS (ELS/AS) affected fear-potentiated startle (fear learning). AS impaired extinction learning ($t(18) = 2.6$, $p = .02$). In adult animals that experienced ELS, extinction learning was similar to controls, but extinction

recall (24 hr after extinction learning) was impaired ($t(18) = 0.16$, $p = .90$). Extinction learning and extinction recall in ELS/AS animals was not different from CTL. In separate experiments, Western blot analyses revealed a significant decrease in GluA1 expression in the IL only following AS ($F(1, 12) = 5.0$, $p = .044$), but neither ELS nor AS changed GluA1 expression in the PL or BLA. In the PL, AS decreased PSD-95 expression ($F(1, 12) = 4.9$, $p = .047$), but ELS significantly increased expression of PSD-95 ($F(1, 12) = 5.7$, $p = .034$). PSD-95 expression in the BLA was unchanged by either ELS or AS. However, there was a significant ELS x AS interaction on the expression of PSD-95 in the IL ($F(1, 12) = 8.2$, $p = .014$), largely driven by a significant increase in PSD-95 expression in the ELS/AS group relative to the other three groups. Overall, these data show that stress changes synaptic proteins important in plasticity in brain areas critical for extinction learning. AS decreased GluA1 in the IL, and those animals were deficient in extinction learning. But ELS increased PSD-95 expression in the IL, which was associated with impaired extinction memory and perhaps masked the learning deficits resulting from decreased GluA1 in the IL. Together, these findings implicate altered GluA1 and PSD-95 expression in the IL as a potential mechanism underlying altered fear behavior following exposure to stress.

Disclosures: M.L. McReynolds: None. **L.C. Ornelas:** None. **N.B. Keele:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.09/JJ4

Topic: F.04. Stress and the Brain

Support: ERA-NET NEURON JTC2013 Grant

Doctoral Program Brain & Mind, University of Helsinki

Title: Identification of biological pathways associated with response to psychosocial stress in the bed nucleus of the stria terminalis in mice

Authors: *Z. MISIEWICZ[1], L. SALMINEN[1], L. RODRIGUES[2], G. MACCARRONE[2], C. REWERTS[2], E. SOKOLOWSKA[1], I. BALCELLS[1], K. TRONTTI[1], S. SAARNIO[1], N. KULESSKAYA[1], M. LAINE[1], S.-A. CALLAN[1], D. GRECO[1], C. TURCK[2], I. HOVATTA[1]
[1]Univ. of Helsinki, Helsinki, Finland; [2]Max Planck Inst. of Psychiatry, Munich, Germany

Abstract: Anxiety disorders are one of the most common mental disorders manifesting as a prolonged and exaggerated response to a threatening situation. They are typically triggered by environmental factors in genetically susceptible individuals. Although the brain regions involved

in anxiety in mammals have been extensively studied, the molecular mechanisms regulating response to stress are still not fully understood. The aim of this study is to determine biological pathways affected by exposure to chronic psychosocial stress in mice through integration of data from transcriptome and proteome analyses.
We used a mouse model of chronic psychosocial stress (social defeat) on two inbred mouse strains, C57BL/6NCrl (B6) and DBA/2NCrl (D2), to induce an anxiety-like response and to establish the resulting protein and gene expression changes in the bed nucleus of the stria terminalis (BNST), a region involved in the stress response. The social preference (SP) behavioral test, carried out after social defeat, showed differences in response to stress between the strains: 24% of B6 and 72% of D2 mice presented social avoidance behavior being susceptible to psychosocial stress. Furthermore, the stress-induced locomotor activity during the SP test within resilient D2 mice was higher than in the susceptible D2 group ($P<0.00$, 37% higher activity). No locomotor differences were observed for the B6 strain. One week after social defeat, we collected the BNST. From half of the samples, we carried out RNA sequencing and identified 543 differentially expressed genes ($P<0.01$, fold change>1.3) when comparing either stress resilient or susceptible mice to controls. We next used the Ingenuity Pathway Analysis (IPA) tool to search for molecular pathways associated with changes in gene expression between these groups. We identified two high-ranking pathways, mitochondrial dysfunction and oxidative phosphorylation, with over-representation of differentially expressed genes in susceptible versus control mice in both B6 ($P=8.73E-12$ and $P=1.55E-11$, respectively) and D2 ($P=5.47E-11$ and 1.59E-09, respectively) strains. The other half of the samples was analyzed for protein expression differences by liquid chromatography–tandem mass spectrometry (LC-MS/MS). For the identification of common molecular targets, we will integrate the RNA and protein expression data and select candidate genes and pathways for functional studies.
Our results suggest that genetic background has a large effect on stress-induced behavior and brain transcriptional response, and provide further insight into understanding the mechanisms underlying individual variability to stress response.

Disclosures: Z. Misiewicz: None. **L. Salminen:** None. **L. Rodrigues:** None. **G. Maccarrone:** None. **C. Rewerts:** None. **E. Sokolowska:** None. **I. Balcells:** None. **K. Trontti:** None. **S. Saarnio:** None. **N. Kulesskaya:** None. **M. Laine:** None. **S. Callan:** None. **D. Greco:** None. **C. Turck:** None. **I. Hovatta:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.10/JJ5

Topic: F.04. Stress and the Brain

Support: NIAAA IRP

Title: Role of the endocannabinoid system in the vmPFC-BLA circuit in fear extinction

Authors: *E. T. BROCKWAY[1], O. GUNDUZ CINAR[1], O. BUKALO[1], A. LIMOGES[1], E. DELPIRE[2], A. HOLMES[1]
[1]Lab. of Behavioral and Genomic Neurosci., Natl. Inst. On Alcohol Abuse and Alcoholism, Rockville, MD; [2]Dept. of Anesthesiol., Vanderbilt Univ. Med. Sch., Nashville, TN

Abstract: Impaired fear extinction is a feature of anxiety disorders and post-traumatic stress disorder. The endocannabinoid (eCB) system has been implicated in anxiety-related behaviors, including fear extinction, via regulation of mechanisms of plasticity in the basolateral amygdala (BLA), such as long-term depression of inhibitory transmission. We have previously demonstrated that optogenetically photoactivating fibers in the BLA arising from the ventromedial prefrontal cortical (vmPFC) facilitates extinction memory formation. Here we sought to extend this observation to the eCB system, first by measuring levels of the eCB, anandamide, in the BLA after vmPFC-BLA photostimulation during extinction. Next, we examined whether systemic blockade of CB1 receptors (CB1R), using the CB1R antagonist, rimonabant, was sufficient to prevented extinction-facilitation by vmPFC-BLA photostimulation. In addition, we selectively deleted CB1R from vmPFC-BLA neurons using an HSV and Flp-dependent viral strategy in a Cnr1-floxed mutant mice. We then used an intersectional approach to selectively manipulate BLA interneurons expressing CB1R - entailing opsin targeting in CCK-Cre/Dlx5/6-flp mutant mice. Taken together, our data provide further insight into the role of the eCB system, acting in the vmPFC-BLA circuit, in mediating fear extinction. Research supported by the NIAAA IRP.

Disclosures: E.T. Brockway: None. **O. Gunduz Cinar:** None. **O. Bukalo:** None. **A. Limoges:** None. **E. Delpire:** None. **A. Holmes:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.11/JJ6

Topic: F.04. Stress and the Brain

Support: The study was sponsored by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany

Title: Effects of Neurexan® on the stress-induced activity of the anterior cingulate cortex

Authors: *I. IZYUROV[1], A. KÜHNEL[2,1], F. YAN[2,3], L. FENSKY[1,2], V. TECKENTRUP[1,4], M. SCHULTZ[5], M. WALTER[1,2,4]
[1]Psychiatry and Psychotherapy, Universitätsklinikum Tübingen, Tübingen, Germany; [2]Clin. Affective Neurosci. Lab., Magdeburg, Germany; [3]Dept. of Psychiatry, CBF, Charité, Berlin, Germany; [4]Leibniz Inst. for Neurobio., Magdeburg, Germany; [5]Biologische Heilmittel Heel GmbH, Baden-Baden, Germany

Abstract: *Background:* Two areas of importance in stress reaction are the anterior cingulated cortex (ACC) and the Amygdala. Previous studies showed that especially the dorsal ACC (dACC) influences the generation of autonomic arousal (Critchley et al., 2003). It was also found that the dACC is activated under cognitive stress (Falkenbeg et al., 2012). Thus, the dACC seems to be an important area controlling stress reactivity. Neurexan®, a medicinal product sold over the counter (OTC), contains four ingredients, Passiflora incarnata (passionflower), Avena sativa (oats), Coffea arabica (coffee) and Zincum isovalerianicum (zinc valerianate). Neurexan® has been investigated in patients with symptoms related to acute stress, nervousness/restlessness, and insomnia. The underlying neuronal mechanisms that lead to the reduction of those symptoms are less clear. In this study we explore whether Neurexan® induces changes in the activation of dACC and associated areas during a stress task.
Method: Thirty-nine healthy male volunteers participated in a randomized, placebo-controlled, double-blind, two-period-crossover trial. The effects of treatment were measured after a single dose of Neurexan or placebo by 3 Tesla fMRI. The stress response was induced using the ScanSTRESS (Streit et al., 2014), which uses arithmetic tasks as well as mental rotation tasks. Additionally the stress response was measured by saliva cortisol concentration and visual analogue scales (VAS) for nervousness and anxiety.
Results: After correcting for multiple testing in the region of interest (right dACC) paired t-test analysis showed a significant activation cluster (peak level p=0.027, FWE-corrected) in rotation stress condition as compared to stress control. Stress induced activity in the right dACC was reduced by Neurexan treatment as compared to placebo. No effect in dACC was found for arithmetics conditions.
Conclusion: The intake of single dose of Neurexan® significantly reduces right dACC activation during psychosocial stress compared to the intake of placebo.
References:
1. *Critchley H.D., Mathias C.J., Josephs O. et al.* 2003 "Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence" *Brain 126.10*, 2139-2152
2. *Falkenberg L.E., Westerhausen R., Specht K. et al.* 2012 "Resting state glutamate level in the anterior cingulate predicts blood-oxygen level dependent response to cognitive control" *Proc. Natl. Acad. Sci. U.S.A. 109.13*, 5069-5073
3. *Streit F., Haddad L., Paul T. et al.* 2014 "A functional variant in the neuropeptide S receptor 1 gene moderates the influence of urban upbringing on stress processing in the amygdala" *Stress 17.4*, 352-361

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Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.12/JJ7

Topic: F.04. Stress and the Brain

Support: Trinity University Neuroscience Department

Title: Extraction of cortisol from marmoset (Callithrix jacchus) and capuchin (Cebus apella) hair as a biomarker of long-term hypothalamic-pituitary-adrenal axis activity

Authors: *A. TUKAN, K. A. PHILLIPS
Trinity Univ., San Antonio, TX

Abstract: As a hormone of the hypothalamic-pituitary-adrenal (HPA) axis, cortisol functions to maintain energy homeostasis and promote anti-inflammation when increased demands challenge the body. Quantifying cortisol provides insight into HPA axis activity and homeostatic conditions of the body. Hair cortisol is a useful biomarker of HPA axis activity because it reflects a cumulative measure of circulating cortisol over time and is independent of circadian rhythm fluctuations. Marmosets (*Callithrix jacchus*) and capuchin monkeys (*Cebus apella*) are New World Primates commonly used in neuroscience research, yet published hair cortisol concentrations for these species are lacking. Hair samples were collected from socially housed marmosets (6 male, 8 female; $n = 14$) and capuchins (2 male, 2 female; $n = 4$) during routine physical exams. Samples were washed in isopropanol, dried, and ground into a fine powder. Methanol was used to extract cortisol from 49g of sample; following extraction samples were centrifuged, and the supernatant was reconstituted using phosphate buffer. Cortisol was quantified using a commercially available enzyme immunoassay kit. The range of hair cortisol concentrations in marmosets was 2614.4-8906.0 pg CORT/mg hair, with a mean ± SEM of 4208.3 ± 443.0 pg/mg. The range of hair cortisol concentrations in capuchins was 621.4-2008.7 pg CORT/mg hair, with a mean ± SEM of 1092.1 ± 337.8 pg/mg. Within each species there was no significant difference in hair cortisol concentration between males and females. The interspecies variation was significantly different, $t(16)= 3.61$, $p=0.002$. These data provide important baseline hair cortisol concentration values for future investigations.

Disclosures: A. Tukan: None. **K.A. Phillips:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.13/JJ8

Topic: F.04. Stress and the Brain

Title: Homeostatic synaptic plasticity in stress circuits

Authors: *N. RASIAH[1], N. DAVIU[2], T.-L. STERLEY[3], T. FUZESI[4], D. G. ROSENEGGER[3], J. S. BAINS[2]
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Abstract: Chronic stress, during which circulating levels of corticosteroids (CORT) are persistently elevated, is a risk-factor for multiple behavioral disorders. PVN CRH neurons, the canonical endocrine controllers of the stress response, also control specific behaviors after a single stress. Here we hypothesized that chronic CORT may re-model synaptic drive to PVN CRH neurons and alter behavioral responses to acute stress.
Mice had access to 25µg/ml CORT in the drinking water for up to 7 days. We then used on-cell and whole-cell electrophysiology to study CRH neuron activity and synaptic properties respectively. Seven-day CORT treatment decreased the firing rate of CRH neurons (0.64Hz ± 0.165 CORT (n=22) vs 2.32± 0.344 naïve (n=24), p=0.0023). There was an increase in mEPSC amplitude (naïve: 21.4 ± 0.8 pA (n=12) vs CORT: 26.1 ± 0.9 pA (n=12), p=0.0026) with no effect on mEPSC frequency, AMPA:NMDA, or PPR. This decrease in activity accompanied by increased glutamatergic strength is consistent with homeostatic changes in synaptic drive that have been reported following persistent activity blockade in cultured cortical neurons. Analysis of the amplitude distributions indicated that these synaptic changes were a consequence of a multiplicative scaling of glutamate synapses. We then asked whether the scaling was a homeostatic response to decreased activity, or if it was due to direct CORT signaling. We used inhibitory hM4Di DREADDs specifically expressed in CRH neurons and administered CNO through drinking water for 7 days. We observed a similar multiplicative scaling of glutamate synapses in CNO treated animals vs hM4Di control (p=0.0071), suggesting that synaptic scaling is a homeostatic response to inactivity. To determine the functional consequences of synaptic scaling, we examined a specific stress behavior, grooming, that is launched by activation of PVN CRH neurons. hM4Di-injected animals were treated with CNO for 7 days and subjected to footshock stress, and their behavior was assessed. We observed a significant increase in grooming time in CNO treated mice (p=0.021) vs control mice.

This is one of few accounts of homeostatic synaptic scaling in adult animals *in-vivo*, and is the first to establish a role for homeostatic plasticity in neural stress circuits.

Disclosures: N. Rasiah: None. **N. Daviu:** None. **T. Sterley:** None. **T. Fuzesi:** None. **D.G. Rosenegger:** None. **J.S. Bains:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.14/JJ9

Topic: F.04. Stress and the Brain

Title: Measuring the activity of hypothalamus CRH neurons during stress

Authors: *T. FUZESI[1], D. G. ROSENEGGER[2], N. RASIAH[4], N. DAVIU[3], J. S. BAINS[3]
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Abstract: Corticotropin-releasing hormone (CRH) synthesizing neurons located in the paraventricular nucleus of the hypothalamus (PVN) control the corticosterone response to stress *via* the hypothalamus-pituitary-adrenal (HPA) axis. The *in vivo* activity of these cells in response to stress has never been directly measured, but was derived from hormone measurements and other indirect consequences of neuronal activity. Thus the time course, amplitude and other properties of the activity is largely unknown. In order to measure the activity of PVN CRH neurons we administered an adeno-associated virus containing a Cre-dependent GCaMP6s construct into the PVN bilaterally. Two weeks later, a 400 um thick optical fiber was implanted above the PVN. *In vivo* fiber photometry experiments started after a subsequent week of recovery and handling. To exclude signal fluctuations due to the animal's movement we used a second light source at a different wavelength as a reference. Mice were exposed to a variety of challenges, including novel environment, footshock, context dependent fear retrieval, fear extinction and a habituated environment. We observed a rapid and robust increases in PVN CRH Ca^{2+} levels in response to footshock and handling which were time locked and showed short duration. Exposure to any, non-homecage environment however, lead to a sudden and prolonged increase of Ca^{2+} that persisted until the animal was returned to the homecage. Interestingly, the amplitude of Ca^{2+} level rise was similar in response to context dependent fear retrieval, and to novel and habituated environment.

Disclosures: T. Fuzesi: None. **D.G. Rosenegger:** None. **N. Rasiah:** None. **N. Daviu:** None. **J.S. Bains:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.15/JJ10

Topic: F.04. Stress and the Brain

Title: Effect of stress controllability on PVN CRH neurons

Authors: *N. DAVIU[1], T.-L. STERLEY[2], N. RASIAH[3], T. FUZESI[4], D. G. ROSENEGGER[2], J. S. BAINS[1]
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Abstract: The ability of an individual to exert control during a stressful event can impact the psychological consequences of traumatic events. In humans, unpredictable and uncontrollable stressful situations increase the risk of developing anxiety related disorders. By contrast, resilience is enhanced in part, by the ability to predict and control stressful events. Similarly, in rodents, inescapable/uncontrollable stress results in hormonal and behavioral responses that are amplified when compared to those observed following controllable stress. This suggest that uncontrollable and controllable stress are differentially processed and remembered, but little is known about the underlying stress related neuronal or circuit dynamics.
We developed a model in which mice were trained for 3 days in an active avoidance task (20 tones + shock (0.3mA) presentation x day). One group could escape or avoid the shock (controllable stress) the other group could not (uncontrollable stress). Analysis revealed less freezing behavior in controllable vs uncontrollable mice in the conditioned context. In addition, the controllable stress group showed a blunted grooming response in the home-cage after stress when compared to uncontrollable stress.
Grooming following stress requires activation of PVN-CRH neurons. To assess the effects of stress controllability on intrinsic excitability, synaptic drive and plasticity in PVN-CRH neurons, we obtained whole-cell recordings 24h after the final stressor exposure. There were no differences in sEPSC frequency or amplitude. There was, however, a striking difference in the ability of glutamatergic synapses to undergo activity-dependent plasticity. Specifically, synaptic potentiation after stress was blunted in the controllable stress group, but not in the uncontrollable stress group.
These data show that behavioral control of a stressful situation impacts subsequent behavior and alters the ability of the synapses to undergo plasticity. This suggests that stress controllability may have protective effects that can be observed at the synaptic level.

Disclosures: **N. Daviu:** None. **T. Sterley:** None. **N. Rasiah:** None. **T. Fuzesi:** None. **D.G. Rosenegger:** None. **J.S. Bains:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.16/JJ11

Topic: F.04. Stress and the Brain

Support: NIH Grant DA042475

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Title: A unique population of stress sensitive neurons in the female bed nucleus of the stria terminalis

Authors: *T. L. FETTERLY[1,2,3,4,5], E. K. AWAD[6], Y. SILBERMAN[7], D. G. WINDER[1,2,3,4,5]
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Abstract: Stress is a major contributor to many psychiatric disorders. Sex is an important biological variable in affective responses to stress. Females have a higher prevalence of diagnosis with affective disorders and anxiety disorders; however, the molecular mechanisms underlying this difference are not well understood. The bed nucleus of the stria terminalis (BNST), a key nucleus in the regulation of affective behavior, is known to be highly sexually dimorphic. The female BNST has been shown to be more stress reactive than the male BNST, as marked by larger increases in *cfos* in female rats following restraint stress. Additionally, female rats have higher numbers of corticotropin releasing factor (CRF) neurons in the BNST than male rats, and these neurons exhibit greater stress responsivity.
We find that neurons expressing CRF in the BNST in mice are also stress responsive as seen by increases in *cfos* expression following acute restraint stress, and that this responsivity is greater in females. To dissect the molecular profile of these stress responsive neurons, we have utilized fluorescent *in situ* hybridization assays to further characterize the enhanced stress-responsivity of BNST CRF neurons in females. Protein kinase C delta (*prkcd*) has been proposed to mark a population of “fear-off” neurons in the extended amygdala, and in males has been shown to largely be expressed in cells distinct from those expressing CRF. We find that following restraint stress, there is a large increase in the number of *crh* expressing neurons that also express *prkcd* in

the BNST of females but not males. Further, we find that this population of co-expressing cells is highly stress-responsive.
To investigate the recruitment of these neurons during stress, we have begun manipulating brain regions that directly project to CRF neurons in BNST. We identified the insula as one such region using channelrhodopsin-assisted mapping, and used a Gi-DREADD expressing virus stereotaxically injected into the insula to look at how inhibition of its activity can alter the stress response seen in the BNST. We found that administering CNO prior to restraint stress blunted the *cfos* upregulation in *crh* cells. However, the upregulation of *prkcd* in *crh* expressing neurons was not altered by this insula manipulation, nor was cfos expression in the co-expressing population. We are currently investigating other CRF cell inputs to see if they contribute to initiating the *prkcd* response. Together, this data suggests that there is a unique population of neurons in the BNST of female mice that is stress sensitive, and that the mechanism for recruitment of these neurons differs as compared to the *crh* population as a whole.

Disclosures: T.L. Fetterly: None. **E.K. Awad:** None. **Y. Silberman:** None. **D.G. Winder:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

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Topic: F.04. Stress and the Brain

Support: FONDECYT Grant N° 1141276 to Alexies Dagnino

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National Doctorate Scholarship, folio number 21140268 to Catherine Pérez Valenzuela

Title: Chronic unpredictable stress enhances 2-4 Hz oscillations in the rat basolateral amygdala during fear behavior

Authors: *C. PÉREZ, M. ARRIAGADA, A. DAGNINO-SUBIABRE
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Abstract: Expression of fear memories is associated with synchronous 4-Hz oscillations in the prefrontal cortex-basolateral amygdala (BLA) circuit. On the other hand, chronic unpredictable stress (CUS) induces both dendritic hypertrophy and affects the inhibitory GABAergic system in BLA. The aim of this study was to analyze in vivo whether chronic stress affects the neuronal activity in BLA during retrieval of fear memory. Male Sprague-Dawley rats were trained in a

classical Pavlovian fear conditioning protocol. Afterward, animals were implanted in BLA with a microelectrode array, following the post-surgery period the animals were subjected to a modified CUS protocol. Local field potentials (LFP) were recorded from BLA during the retrieval of fear memory using a wireless multi-channel recording system. We found that during retrieval of fear memory, power of 2-4 Hz oscillations from BLA was enhanced specifically during freezing behavior, a physiologically conditioned response to fear. Seven days after retrieval, 2-4 Hz oscillations from BLA decreased in control animals, however, it is remains enhanced in the rats that were subjected to CUS protocol. Our results suggest that extinction of fear memory could be related to decreasing of power of 2-4 Hz oscillations from BLA, while enhancing of 2-4 Hz oscillations after CUS could be related to persistence of fear memory in chronically stressed animals.

Disclosures: C. Pérez: None. **M. Arriagada:** None. **A. Dagnino-Subiabre:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.18/JJ13

Topic: F.04. Stress and the Brain

Title: Glucocorticoid and nitric oxide regulation of membrane trafficking of the alpha-1 adrenergic receptor in hypothalamic neurons

Authors: *G. L. WEISS[1], V. J. DANIEL[1], J. G. TASKER[2]
[2]Cell and Mol. Biol., [1]Tulane Univ., New Orleans, LA

Abstract: Glucocorticoid negative feedback in hypothalamic neuroendocrine cells is crucial for maintaining homeostasis and avoiding stress-related disorders. Inhibitory transcriptional regulation of hypothalamic neurons by glucocorticoids has been well characterized. Here we focus on the rapid mechanisms by which glucocorticoids downregulate hypothalamic neuronal activity by desensitization of the excitatory effect of norepinephrine. Activated alpha-1 adrenergic receptors on corticotropin releasing hormone (CRH) neurons dramatically increase excitatory synaptic inputs through stimulation of a retrograde messenger, making norepinephrine excitatory via the retrograde activation of upstream glutamate neurons. Glucocorticoids rapidly desensitize the CRH neurons to norepinephrine by inducing internalization of alpha-1 receptors by an unknown mechanism. Nitric oxide is involved in several aspects of GPCR trafficking and was tested as a likely signal mediating glucocorticoid-induced internalization of alpha-1 receptors. We found that the nitric oxide synthase inhibitor LNAME, like corticosterone, was sufficient to induce alpha-1 receptor internalization. Co-application of LNAME and corticosterone had no additive effect, suggesting that the two treatments work by the same

mechanism. Tracking of subcellular trafficking of internalized alpha-1 receptors was also performed using Rab proteins as markers of the endocytic pathway. Interestingly, corticosterone had no effect on alpha-1 receptor interaction with the early endosomal marker Rab5, despite the increased internalization. These data suggest that glucocorticoids do not increase the rate of alpha-1 receptor internalization, but perhaps sequester receptors that would normally be recycled back to the membrane. Additional analysis of intracellular trafficking of the alpha-1 receptor could reveal a novel mechanism by which a steroid hormone can regulate the activity of a GPCR.

Disclosures: G.L. Weiss: None. **V.J. Daniel:** None. **J.G. Tasker:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.19/JJ14

Topic: F.04. Stress and the Brain

Support: NIH 2R01 MH066958

Title: Norepinephrine stimulates dendritic vasopressin release from CRH neurons to activate a retrograde neuronal-glial circuit

Authors: *C. CHEN[1], Z. JIANG[2], J. G. TASKER[3]
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Abstract: Corticotropin releasing hormone (CRH) neurons of the hypothalamic paraventricular nucleus (PVN) release CRH as an initiating signal in the hypothalamic-pituitary-adrenal (HPA) response to stress. CRH neurons in the PVN are activated by ascending noradrenergic projections mainly from the A2 cell group in the caudal nucleus of the solitary tract. Our previous findings revealed that the noradrenergic modulation of PVN CRH neurons is mediated by a α_1-adrenoceptor-induced activation of a retrograde neuronal-glial circuit that results in the stimulation of presynaptic glutamate and GABA neurons. Release of a retrograde messenger from the CRH neurons causes an increase in calcium concentration in neighboring astrocytes and the astrocytic release of ATP which activates local glutamate and GABA neurons and causes an increase in spike-dependent glutamate and GABA release onto the CRH neurons. To determine the retrograde messenger involved in the norepinephrine (NE) stimulation of glutamate and GABA inputs to CRH neuron, we performed whole-cell patch clamp recordings, calcium imaging, pharmacological and genetic manipulations in CRH neurons in slices from a CRH-eGFP mouse. The NE-induced increase in synaptic inputs to CRH neurons was not blocked by

the type 1 CRH receptor antagonist antalarmin. The NE effect was, however, blocked by the vasopressin V1a receptor antagonist SR49059, and was mimicked by local application of vasopressin, suggesting it was mediated vasopressin release. Vasopressin application was caused a calcium response in astrocytic calcium. A control experiment was performed to show that the PVN astrocytic V1a receptor activation was not caused by the dendritic release of vasopressin from vasopressin neurons. These findings suggest, therefore, that NE stimulates vasopressin release, from CRH neurons, dendrites to activate a retrograde astrocyte circuit that stimulates return excitatory and inhibitory synaptic inputs to the CRH neurons. Supported by NIH 2R01 MH066958

Disclosures: C. Chen: None. **Z. Jiang:** None. **J.G. Tasker:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 070.20/JJ15

Topic: F.04. Stress and the Brain

Title: Chronic unpredictable stress modulates neuronal activity of AgRP and POMC neurons in hypothalamic arcuate nucleus

Authors: *X. FANG, J. WANG, Z. ZHANG, Y. LEI, X.-Y. LU
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Abstract: Chronic unpredictable stress (CUS) induces depressive-like behavioral phenotypes in mice, such as anhedonia. The arcuate nucleus of the hypothalamus is a key brain region in the regulation homeostatic and hedonic feeding. It contains two intermingled populations of neurons expressing proopiomelanocortin (POMC) and agouti-related protein (AgRP). Our previous studies have shown that POMC and AgRP neurons are differently regulated by acute emotional stress (Liu et al., 2007). The goal of this study was to investigate the effects of chronic stress on neuronal activity and plasticity of POMC and AgRP neurons. *Agrp-IRES-Cre* mice and *Pomc-Cre* were crossed with *Ai14* mice to produce *Agrp*-ires-*cre;tdTomato* and *pomc-cre;tdTomato* reporter mice. Electrophysiological recordings were made from identified arcuate nucleus AgRP and POMC neurons in brain slices of reporter mice after exposure to 10 days of CUS or control procedures. We found that CUS deceased the firing rate of AgRP neurons but increased the firing rate of POMC neurons in both male and female mice. The effects of CUS on excitatory and inhibitory synaptic inputs onto AgRP and POMC neurons are currently under investigation. Our results suggest that the changes in neuronal activity of arcuate nucleus AgRP and POMC neurons may mediate chronic stress-induced depressive behaviors.

Disclosures: **X. Fang:** None. **J. Wang:** None. **Z. Zhang:** None. **Y. Lei:** None. **X. Lu:** None.

Poster

070. Stress-Modulated Pathways: Molecular, Endocrine, and Electrophysiological Outcomes

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: F.04. Stress and the Brain

Support: Nu Rho Psi Undergraduate Research Grant 2017

Title: Epigenetic pathways of stress sensitivity and resilience

Authors: *V. KREOUZIS[1], G. M. MILLER[2]
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Abstract: Stress exacerbates many diseases, and understanding its molecular mechanisms is crucial to the development of novel therapeutic interventions to combat stress-related disorders. The driver of the stress response in the Hypothalamic-Pituitary-Adrenal Axis (HPA) is Corticotrophin Releasing Hormone (CRH), a neuropeptide synthesized in the Paraventricular Nucleus of the Hypothalamus. Evidence supports that CRH expression is epigenetically modified at the molecular level by environmental stimuli, causing changes in the stress response. This effect is mediated by a concert of factors that translate environmental change into alteration in gene expression. An important regulator and epigenetic modulator of CRH expression is Neuron Restrictive Silencing Factor (NRSF). Previously, our lab identified numerous splice variants of NRSF that are specific to humans and predictive of differential regulatory effects on targeted gene expression. Human cell lines BeWo and ARPE19 have endogenous CRH and NRSF expression and accordingly, we are using these cell lines to study the effects of NRSF isoforms on CRH expression. Both NRSF and CRH are CRE-responsive genes, and so we are also investigating the effects of activation of the cAMP pathway on CRH and NRSF expression and splicing. Through overexpression or knockdown of specific NRSF isoforms, we seek to understand the effects of NRSF variants on CRH expression. To date, we have verified that BeWo and ARPE19 cells express CRH using real time PCR, and our preliminary data shows that CRH expression is upregulated by 250 micromolar 8-Br-cAMP in a time-dependent manner in both cell lines. By using PCR primers within exonic boundaries of NRSF, we have found evidence for multiple NRSF splice variants in both cell lines. Preliminary findings indicate that the two cell lines differ in their expression levels of CRH. Future studies using anti-sense morpholino oligonucleotides to control the expression pattern of NRSF splice variants will explore downstream effects on CRH gene expression.

Disclosures: **V. Kreouzis:** None. **G.M. Miller:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.01/JJ17

Topic: D.03. Somatosensation: Pain

Support: DoD W81XWH-14-GWIRP-IIRA/GW120066

University of Florida Foundation

Title: Molecular maladaptations to vascular nociceptor $Na_v1.9$ covaries with exposure to pyridostigmine bromide in a rat model of gulf war illness pain

Authors: *B. Y. COOPER[1], T. J. NUTTER[2], L. K. FLUNKER[4], R. D. JOHNSON[3]
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Abstract: Introduction. Many veterans of Operation Desert Storm (ODS) still struggle with symptoms of GWI. Symptoms are manifested as diverse cognitive, motoric and sensory abnormalities that include chronic pain. In order to understand the pathophysiology of GWI pain, our laboratory has developed rat models of this multisymptom disorder.
Method. We examined the influence of 4 GW agents on the ambulatory and resting behaviors of rats. Young adult male rats were exposed to either 3 or 4 GW chemicals for a period of 4 weeks. One group was exposed to DEET (400 mg/kg; topical, 50%), permethrin (2.6 mg/kg; topical), chlorpyrifos (120 mg/kg; s.c.) and pyridostigmine bromide (PB, 13 mg/kg; oral; GRP A, n=56). A second group received the same exposure but PB was excluded from the protocol (GRP PB, n=10). A third group served as a vehicle control (Grp C, n=28; ethanol topical, corn oil s.c., and water gavage). Ambulation and resting scores were measured weekly by an automated infrared detection system. Nine weeks after exposure, thirty rats received treatments intended to ameliorate deep tissue pain (Riluzole, 3 mg/kg; Retigabine, 7 mg/kg; 14 days). Sixteen weeks after chemical exposures ended, an additional 34 rats were euthanized, and their dorsal root ganglia prepared for whole cell patch studies. ANOVA was used to assess changes in rat behaviors due to exposures and treatments. Student t tests were used to assess molecular data.
Results. Rats exposed to 4 GW chemicals (GRP A) developed pain-like deficits in ambulation and resting that persisted 13-16 weeks post-exposure (16 WP; $p<.001$ and $p<.001$, respectively). Rats exposed to only 3 GW agents (PB excluded) did not exhibit pain-like signs in weeks 13-16. Compared to vehicle exposed rats (GRP C), the amplitude of vascular, but not muscle nociceptor $Na_v1.9$ was elevated in GRP A (16WP; $p<.02$); but K_v7 activity was unchanged. When PB was excluded from the exposure (GRP PB) vascular nociceptor $Na_v1.9$ amplitude was similar to controls and significantly reduced relative to neurons harvested from GRP A rats (16 WP;

p<.005); Treatment with $Na_v1.9$ inhibitor, Riluzole, did not improve behavior scores at 9-10WP; but K_v7 opener Retigabine did produce positive trends (p<.07).
Conclusion. Exposure to PB was critical for the emergence of persistent pain signs in a rat model of GWI. Maladaptations of vascular, but not muscle nociceptor, $Na_v1.9$, covaried with the manifestation of pain-like behaviors. Treatments targeting $Na_v1.9$ were not effective at 10WP.

Disclosures: B.Y. Cooper: None. **T.J. Nutter:** None. **L.K. Flunker:** None. **R.D. Johnson:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.02/JJ18

Topic: D.03. Somatosensation: Pain

Support: DoD Grant GW140066

Title: Long-term increases in hindlimb vasodilatation following exposure to Gulf War Illness (GWI) chemical prophylactic agents is independent of cardiovascular parameters and suggests involvement of CGRP release from vascular nociceptor endings in a rat model of GWI pain

Authors: C. M. TOURNADE[1], H. D. NGUYEN[1], B. Y. COOPER[2], *R. D. JOHNSON[3]
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Abstract: Gulf War veterans experienced high levels of exposure to insecticides/repellants and nerve gas chemoprophylactic agents, which resulted in a series of chronic clinical symptoms (i.e. Gulf War Illness) including unusual complexes of headache, joint, muscle and abdominal pain. We previously developed a rat model of GWI pain produced by a 4-week exposure to four GWI chemical agents, measurements of ambulatory/resting behaviors during the exposure and the 16W post exposure period, and determination of electrophysiological profiles of single vascular nociceptors. In the present study, we hypothesized that GWI chemical-induced maladaptations in vascular afferents (shown by our previous data) would produce increased peripheral release of their predominant constitutive vasodilatory neuropeptide, CGRP, resulting in subsequent vasodilatation and increased detectable blood flow. This study used a noninvasive laser scanning contrast imaging (LSCI) to measure hindpaw blood flow. Young adult male rats were exposed to either (i) DEET (400 mg/kg; topical, 50%), permethrin (2.6 mg/kg; topical), chlorpyrifos (s.c.; 120 mg/kg) and pyridostigmine bromide (PB,13 mg/kg; oral; GRP A, n=16), (ii) all chemicals except for PB (GRP PB, n=14), or (iii) vehicle control (Grp C, n=16; ethanol topical, corn oil s.c., and water gavage). Before and every two weeks after chemical exposure, rats were briefly anesthetized with isoflurane (10-15min) and blood flow in the plantar hindpaws recorded for five

minutes with a PeriCam LSCI laser probe. The analysis area was set by programmable software based on spatial landmarks and was used for all animals to validate inter-animal and within-animal comparisons. Cardiovascular parameters of tail cuff blood pressure (systolic and mean arterial pressures), heart rate, and temperature (body core and hindpaw) were also measured. There were highly significant increases in hindpaw blood flow (vasodilatation) at post exposure weeks 4-10 ($p<0.01$) in GRP A rats compared to GRP C controls, corresponding to behavioral measures of pain, despite the lack of differences in cardiovascular measures of blood pressure, heart rate, and temperature. Interestingly, the GRP PB rats that lacked exposure to PB, did not show increased blood flow during the post exposure period. We conclude that in animals exposed to the four GW chemicals, long-term increases in blood flow (vasodilatation) were produced for at least 8 weeks after the exposure period, and in the absence of changes in cardiovascular parameters, suggests that hyperactivity in vascular afferents leads to increased release of vasodilator neuropeptides (e.g. CGRP) from the terminal endings.

Disclosures: C.M. Tournade: None. **H.D. Nguyen:** None. **B.Y. Cooper:** None. **R.D. Johnson:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.03/JJ19

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: W81XWH-16-2-0058

Title: Effect of Gulf War “Desert-Dust” compounds on the viability and permeability of the blood-brain barrier in a 3D model

Authors: *J. F. HOFFMAN[1], C. E. KASPER[2], J. F. KALINICH[1]
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Abstract: Gulf War Illness (GWI) refers to the chronic multi-symptom illness characterized by cognitive problems, fatigue, and muscle pain suffered by over one-third of American veterans who served in the Persian Gulf War in 1990-1991. Investigations into potential causes suggest a multiple exposure scenario, possibly to a combination of the nerve gas prophylactic pyridostigmine bromide (PB), insecticide N,N-diethyl-*m*-toluamine (DEET), and pesticide permethrin (PM), rather than a single exposure incident. Experiments have shown combining exposures to PB with PM or DEET disrupts the blood-brain barrier (BBB) and causes neurological and behavioral deficits, but does not account for all reported symptoms of GWI. Another study suggests PB alone can increase BBB permeability, allowing a virus to cross over

into the brain where it is not normally found. Other studies suggest that respiratory exposure to the fine-grained sand particles found in the area, deemed “desert dust,” could also be linked to GWI. Analysis of this desert dust found high levels of a variety of metals, including aluminum, iron, uranium, nickel, cobalt, copper, strontium, manganese, and zinc. Under certain conditions, metals have been known to cross the BBB into the brain and induce neuronal injury and behavioral changes. We hypothesize that combined exposures of PB, PM, and DEET adversely affect BBB permeability, allowing metals solubilized from inhaled desert dust particles to enter the brain. To test this, we used a combination of traditional cell culture and a 3D dynamic *in vitro* model of the BBB (DIV-BBB). First, human brain endothelial cells (Cell Systems, ACBRI 376) and human astrocytes (Lonza, CC-2565) were individually exposed to PB, PM, DEET, nickel, cobalt, strontium, zinc, manganese, copper, iron, aluminum, or depleted uranium (dose range 0.1 to 1000 µM) and assessed for viability and function using standard cell culture techniques. For most compounds, we found 1 µM to be a sufficiently sub-toxic dose, which was then used in the 3D DIV-BBB system (FloCel). Endothelial cells in the luminal (blood) side of a 3D cartridge were co-cultured with astrocytes in the abluminal (brain) side of the cartridge, and allowed to establish tight junctions evidenced by a high transendothelial electrical resistance (TEER) value. The closed system, which provided a more realistic model of blood flow and metabolite exchange across a BBB, was exposed to sub-toxic levels of PB, PM, and DEET for 24 hours, followed by sub-toxic levels of each metal and monitored for changes in TEER and the translocation of metal from the luminal to abluminal side.

Disclosures: **J.F. Hoffman:** None. **C.E. Kasper:** None. **J.F. Kalinich:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.04/JJ20

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CDMRP Grant GW080150

CDMRP Grant GW120037

CDC-NIOSH NORA Grant

Title: Microglia play a crucial role in the neuroinflammation underlying Gulf War Illness

Authors: *L. T. MICHALOVICZ, K. A. KELLY, J. V. MILLER, D. B. MILLER, J. P. O'CALLAGHAN
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Abstract: Gulf War Illness (GWI) is a multi-symptom disorder exhibiting many features that are similar to sickness behavior. We have established that, like sickness behavior, GWI is associated with underlying neuroinflammation. In particular, exposures experienced by soldiers during the Gulf War, such as physiological stress, pesticides and nerve agents, have led to a chronic, primed neuroinflammatory state that results in an exacerbated response to subsequent inflammatory challenges. The observation that neuroinflammation and neuroinflammatory priming may be the underlying cause of GWI indicates that this illness may be the result of long-term alterations in the brain's resident immune cells, microglia and astrocytes. Here, we have investigated the potential involvement of microglia in GWI using a genetically modified mouse strain, CX3CR1 -/-, and minocycline, an anti-inflammatory drug with effects on microglia. Adult male C57BL/6J or CX3CR1 -/- mice were exposed to our GWI model consisting of corticosterone (CORT) in the drinking water at levels associated with high physiological stress for 7 days followed by an exposure to the nerve agent surrogate, diisopropyl fluorophosphate (DFP), on day 8 and a subsequent immune challenge with lipopolysaccharide (LPS) on day 10. C57BL/6J mice that were given minocycline received a single dose 30 minutes prior to LPS. To test whether minocycline or CX3CR1 -/- disrupted LPS-induced inflammation, an additional cohort of animals were exposed to CORT for 7 days followed by an LPS exposure on day 8. Interestingly, despite the potent cytokine expression induced by CORT+LPS exposure, neither CX3CR1 -/- nor minocycline-treated mice exhibited major differences in cytokine mRNA expression compared to controls. However, both CX3CR1 knockout and minocycline treatment removed the contribution of DFP to the GWI neuroinflammatory profile, reducing cytokine mRNA expression to levels comparable to CORT+LPS treatment. The recovery of the GWI phenotype to CORT+LPS levels is highly significant, because this condition mimics a "healthy sick" state in which stress may potentiate inflammatory conditions. These results suggest that not only do microglia play a crucial role in the development/maintenance of GWI, but also that DFP exposure in particular seems to cause alterations in normal microglial functioning. Furthermore, this study indicates that treatments that have modulatory effects on microglia, like minocycline, show promise for the restoration of homeostatic sickness behavior in veterans suffering with GWI.

Disclosures: L.T. Michalovicz: None. **K.A. Kelly:** None. **J.V. Miller:** None. **D.B. Miller:** None. **J.P. O'Callaghan:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.05/JJ21

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Department of Defense Grant GWI140097

Title: Altered Von Frey pain thresholds in a model of gulf war illness is restored by vagus nerve stimulation

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Abstract: Gulf war Illness (GWI) refers to a chronic complex of symptoms observed in a large percentage of men and women who served in the Persian Gulf War. GWI symptoms include memory and concentration problems, headaches, migraines, widespread pain, fatigue, gastrointestinal and respiratory issues, and other abnormalities that do not fit into classical medical diagnoses. Considering the chronic pain that is often reported in GWI patients, we sought to determine if, in a mouse model of GWI, afflicted mice would experience altered pain thresholds in the von Frey nociception assay.
Methods: All protocols were approved by the Baylor Scott and White IACUC. GWI was induced in CD1 mice, by 10 daily injections of permethrin and pyrostigmine bromide. Reactivity to von Frey stimulation was assessed as follows: progressively stronger tactile stimuli (von Frey stimuli formed from nylon monofilaments) was applied sequentially to the plantar surface of the paw until subjects exhibit a paw withdrawal (motor response) or flexion response. Each subject was tested twice on each paw in a counterbalanced ABBA order, with each test separated by a 2 minute interval. Tactile data were reported using the linear monofilament number scale provided by the manufacturer: Intensity = log10 (10,000 × g), assuming linearity for ANOVA. All tactile testing was performed by raters blind to experimental conditions. At 9 months after GWI induction, vagus nerve stimulators were implanted around the left carotid sheath, and mice were continuously stimulated for 2 or 4 weeks.
Results: The results show that within two months after the induction of GWI, mice exhibited increased tactile sensitivity with lower paw withdrawal threshold, compared to age matched controls, and compared to older mice at 10 months after the induction of GWI. These latter mice exhibited a hyposensitive paw withdrawal threshold compared to age matched controls. Interestingly, vagus nerve stimulation restored the normal withdrawal response at this later time point, to a level similar to naïve controls of same age.
Conclusion: Administration of Gulf War chemicals to a mouse results in a behavioral and physiological phenotype that is analogous to human GWI. Using this model, we observed increased withdrawal response within 2 month after GWI induction, and decreased withdrawal response at 10 months after induction. We suggest that the chronic response may involve compensatory mechanisms such that the mice have adapted to chronic pain, resulting in a reduced withdrawal response at the latter time point. Moreover, vagus nerve stimulation initiated at 9 months after GWI induction restored the withdrawal response in the GWI affected mice.

Disclosures: L.A. Shapiro: None. **J.W. Grau:** None. **D. Nizamutdinov:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

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Program#/Poster#: 071.06/JJ22

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CDMRP W81XWH-15-1-0433

CDMRP W81XWH-13-2-0072

NIH R01DA031900

NIH R01NS28785

Title: Sub-threshold exposure to sarin negatively affects neuronal microtubules in a manner exacerbated by stress: Implications for Gulf War Illness

Authors: *A. PATIL[1], A. N. RAO[1], Z. D. BRODNIK[1], L. QIANG[1], R. A. ESPAÑA[1], K. A. SULLIVAN[2], M. M. BLACK[3], P. W. BAAS[1]
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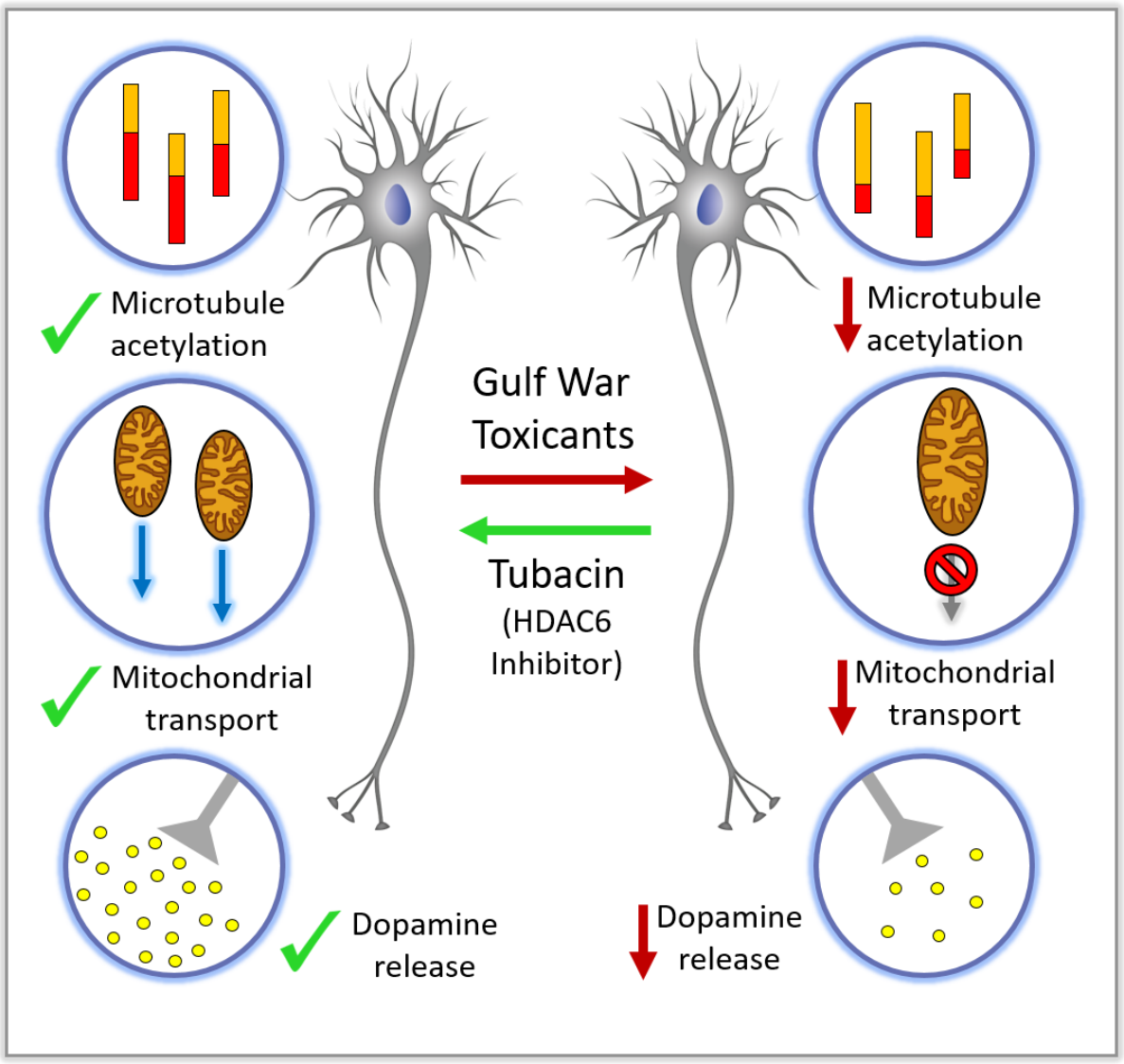
Abstract: Recent work has identified the use of organophosphates (OP) such as Sarin and N,N-Diethyl-meta-toluamide (DEET) in the 1990-91 Persian Gulf War as being causally related to the development of Gulf War Illness (GWI), a multi-symptom illness experienced by deployed veterans. Prior culture work has shown deficits in axonal transport after OP exposure, however, these studies did not account for the elevated levels of stress hormones experienced by Gulf War veterans. In our studies, we treated rat cortical and fetal ventral mesencephalic neurons with diisopropylfluorophosphate (DFP), a Sarin gas analog, in conjunction with corticosterone (CORT) pretreatment. CORT pretreatment was administered to mimic the elevated level of stress hormones that would present in soldiers in war zones. Using this paradigm, we assessed changes in microtubule stability, mitochondrial dynamics, and neurotransmitter release. Western blot analysis showed that microtubule stability was affected, as evidenced by a decrease in the acetylated (stable) tubulin fraction after treatment. Additionally, microtubule polymerization, observed by ectopic expression of the plus-end binding protein EB3 conjugated to GFP, was diminished after DFP exposure. Using the mitochondrial-dye Mitotracker, we imaged the microtubule-based transport of mitochondria in living neurons. After DFP exposure, mitochondrial transport was significantly reduced. After DFP treatment, deficits were also observed in the levels of dopamine released from neurons isolated from the ventral mesencephalon (dopaminergic precursors). Interestingly, the effects of DFP were exacerbated in

all parameters after CORT pretreatment. We sought to rescue cells from the effects of OP exposure by treating them with tubacin, an HDAC6 inhibitor, and saw notable improvement in MT stability, mitochondrial transport, and neurotransmitter release.



Disclosures: **A. Patil:** None. **A.N. Rao:** None. **Z.D. Brodnik:** None. **L. Qiang:** None. **R.A. España:** None. **K.A. Sullivan:** None. **M.M. Black:** None. **P.W. Baas:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.07/JJ23

Topic: F.04. Stress and the Brain

Support: VA Grant 1101 BX001374 (MAW)

VA Grant I21 BX002085 (LPR)

University of South Carolina School of Medicine Research Development Fund (LPR)

VA Grant IO1 BX001804 (LPR)

NIH Grant AG050518 (JRF)

Title: Effects of stress and pyridostigmine bromide on acetylcholine and glutamate in the rat prefrontal cortex and hippocampus

Authors: *V. A. MACHT[1,2], J. L. WOODRUFF[3,2], E. S. MAISSY[3], C. A. GRILLO[3], M. A. WILSON[3,2], J. R. FADEL[3], L. P. REAGAN[3,2]
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Abstract: Veterans from the 1990-1991 Gulf War report clusters of medically unexplained symptoms after being prophylactically administered the acetylcholinesterase inhibitor pyridostigmine bromide (PB) to protect against toxic effects of nerve gas exposure. However, recent evidence has suggested that the combinations of PB and stress of deployment may have had unexpected detrimental effects on the nervous system. To test this hypothesis, the current study used a rat model of Gulf War Illness where Sprague Dawley rats were treated by gavage with either vehicle or 1.3 mg/kg PB for 14 days. On days 5-14 during vehicle/PB treatment, rats were subjected to restraint stress (6 hrs/day) or handled (non-stress control). One week later, *in vivo* microdialysis was performed to examine how combinations of PB and repeated restraint stress impacted cholinergic and glutamatergic neurotransmission in the prefrontal cortex (PFC) and hippocampus following an acute restraint stress challenge. Results indicate that an acute restraint stress challenge increases both acetylcholine and glutamate in the hippocampus in all rats without prior stress history. Acetylcholine levels are also increased in the PFC following an acute restraint challenge in all rats without prior stress history; this cholinergic response to stress is blunted in the PFC but not hippocampus in rats with prior stress history. Conversely, a prior stress history depresses glutamatergic release in the hippocampus in vehicle but not PB-treated rats. These results indicate cholinergic and glutamatergic systems in the PFC and hippocampus are differentially impacted by stress and PB treatment which may have important implications for stress-induced changes in cognitive function. *Supported by Department of Veterans Affairs grant numbers 1101 BX001374 (MAW), I21 BX002085 (LPR), IO1 BX001804 (LPR) and the University of South Carolina School of Medicine Research Development Fund (LPR)*

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Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

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Program#/Poster#: 071.08/JJ24

Topic: F.04. Stress and the Brain

Support: VA grant I21 BX002085

VA grant IO1 BX001804

AHA grant 15SDG22430017

Title: Cardiovascular changes elicited by stress and pyridostigmine bromide in a rat model of gulf war illness

Authors: *L. P. REAGAN[1], J. WOODRUFF[2], V. A. MACHT[5], J. RIVERS[2], C. A. GRILLO[3], B. MUNIZ[2], C. M. LOMBARD[4], S. K. WOOD[1]
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Abstract: Pyridostigmine Bromide (PB), an acetylcholinesterase inhibitor used as a prophylactic agent against nerve gas during the Gulf War, has been suggested as a possible cause of the chronic constellation of symptoms suffered by Gulf War Veterans. Under non-stressful laboratory conditions PB was demonstrated to have minimal autonomic consequences, however it is suggested that when combined with repeated stress PB may be deleterious to the autonomic system, contributing to GWI symptomatology. In the present study male rats were treated with either vehicle or PB (1.3 mg/kg) daily for 14 consecutive days. On the final 10 days of treatment, rats were exposed to either 6 hours of restraint stress or non-stressed control. To identify the dynamic temporal development of autonomic changes, cardiovascular telemetry was used to measure blood pressure (mean arterial pressure; MAP) and heart rate (HR) at an acute, early time point and a delayed time point (3 months post stress/treatment). Acute PB treatment resulted in a transient increase in MAP 30-60 mins following the 1st PB injection. Alternatively, upon the first stress exposure, when acetylcholinesterase (AchE) activity is reduced by approximately 50%, PB blunted the hemodynamic and tachycardic response to restraint stress compared with vehicle treatment. Moreover, when challenged with an injection of lipopolysaccharide (LPS, 100μg/kg) 9 days after the last stress/treatment, rats with a history of stress and PB treatment demonstrated a blunted LPS-induced pressor and tachycardic response compared with PB-treated controls. In contrast to PB's acute actions, , the effect of prior PB treatment on AchE activity at the delayed timepoint is distinct from that of the acute measurements, as evidence of elevated AchE levels emerge. These data acquired at the delayed timepoint are consistent with studies in GWI patients

that demonstrate evidence of deficient vagal acetylcholine tone. Ongoing studies are further identifying the autonomic changes that have emerged at rest and during subsequent stress challenges in PB versus vehicle-treated rats with a history of stress or control. Taken together, these studies shed considerable insight into the distinct autonomic effects of PB treatment during repeated stress exposure as compared with treatment under non-stress conditions.

Disclosures: L.P. Reagan: None. **J. Woodruff:** None. **V.A. Macht:** None. **J. Rivers:** None. **C.A. Grillo:** None. **B. Muniz:** None. **C.M. Lombard:** None. **S.K. Wood:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.09/JJ25

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: 5U54NS083924-03

Title: A tobacco cembranoid has neuroprotective effect against neurotoxicants involved in the Gulf War Illness

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Abstract: Organophosphate (OP) compounds have been widely used as agricultural and household pesticides, jet engine lubricants, and warfare nerve agents. Therefore, the general population and military personnel could be exposed to OPs not only during combat or terroristic attacks but also during routine military, industrial or private activities. The acute effect of high dose of OPs is characterized by life-threatening seizures due to overstimulation of central mAChR, excessive release of glutamate followed by axonal loss and neuronal degeneration. A delayed neuronal damage of the OP intoxication is thought to contribute to neuronal death and various neurological illnesses. Gulf War Illness (GWI) is one of them. GWI is a currently untreatable multi-symptom disorder experienced by more than 250,000 veterans from the Persian Gulf War (1990-1991). The distinctive hallmark of GWI includes chronic fatigue, migraine, muscle and joint pain, gastrointestinal problems and cognitive disturbances such as depression and anxiety. Various studies have consistently linked these symptoms to the exposure to pyridostigmine, DEET, permethrin and traces of sarin (the most commonly used nerve agent). There is no effective cure for the GWI or the chronic effect of other neurotoxicants. Our group demonstrated in vitro that exposure to diisopropylfluorophosphate (DFP, a surrogate of sarin) and the above mentioned neurotoxicants reduce the number of functionally active neurons in hippocampal slices. This loss of neuronal functionality can be reversed by application of a 4R-cembranotrienes-diol (4R), a cyclic diterpenoid, with anti-inflammatory and anti-apoptotic

properties. The cembranoid is not toxic and reaches higher concentrations in the brain than plasma. We took advantage of our in vitro GWI model (rat hippocampal slices) to investigate whether 4R has a protective effect on synaptic integrity and neuronal survival in the presence of DFP. We combined electrophysiological recordings with molecular, histological and ultrastructural analysis on acute hippocampal slices. The cembranoid protects the integrity of dendrites and reduces the activation of astrocytes. In conclusion, the tobacco cembranoid is a promising compound to protect the nervous system against neurotoxicants.

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Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.10/JJ26

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: U.S. Department of Veterans Affairs

University of Minnesota

Title: Subcortical brain volume reduction in Gulf war illness

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Abstract: Introduction: Gulf War Illness (GWI) is a multisystem disorder affecting a substantial number of veterans who served in the 1990-91 Gulf War. The brain is predominantly affected, as manifested by the presence of neurological, cognitive and mood symptoms. Although brain dysfunction in GWI has been well documented, abnormalities in brain structure have been debated.
Method: We calculated the volume of 35 left cortical areas, 35 right cortical areas, 8 left subcortical areas, 8 right subcortical areas, the brainstem, and total intracranial volume in 28 (27 men) control GW veterans and 46 (43 men) veterans suffering from GWI, as determined by Center for Disease Control and Kansas criteria, and without mental health comorbidities. Participants underwent a high-resolution structural Magnetic Resonance Imaging (sMRI) using the Philips 3T MR scanner at the Minneapolis VA Medical Center. For each participant, high resolution T1- and T2-weighted anatomical images were processed using the Human

Connectome Project version of FreeSurfer to extract the brain volumes.
Results: We report a substantial (~10%) subcortical brain atrophy in GWI comprising mainly the brainstem, cerebellum and thalamus, and, to a lesser extent, basal ganglia, amygdala and diencephalon. The highest atrophy was observed in the brainstem, followed by left cerebellum and right thalamus, and by the right cerebellum and left thalamus. These findings indicate graded atrophy of regions anatomically connected through the brainstem via the crossed superior cerebellar peduncle (left cerebellum to right thalamus, right cerebellum to left thalamus). This distribution of atrophy is accompanied by observed systematic reduction in volume of other subcortical areas (basal ganglia, amygdala and diencephalon).
Conclusions: Our observed distribution of atrophy resembles toxic encephalopathy caused by substances such as organic solvents. Given the potential exposure of Gulf War veterans to "a wide range of biological and chemical agents including sand, smoke from oil-well fires, paints, solvents, insecticides, petroleum fuels and their combustion products, products, organophosphate nerve agents, pyridostigmine bromide, ⋯", it is reasonable to suppose that such exposures, alone or in combination, could underlie the subcortical atrophy observed.

Disclosures: P.S. Christova: None. **L.M. James:** None. **B.E. Engdahl:** None. **S.M. Lewis:** None. **A.F. Carpenter:** None. **A.P. Georgopoulos:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.11/JJ27

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Assistant Secretary of Defense for Health Affairs through the Congressionally Directed Gulf War Illness Research Program (W81XWH-16-1-0626)

Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development, Rehabilitation Research and Development (I01RX001520))

The Florida Department of Health James and Esther King Biomedical Research Program (4KB14)

The Bay Pines Foundation

Title: Exposure to pyridostigmine bromide, DEET, and chlorpyrifos in a mouse model of Gulf War Illness

Authors: *B. A. CITRON[1,2], D. C. DRISCOLL[1], W. A. RATLIFF[1,2]
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Abstract: Approximately 25-35% of veterans who served in the 1990-1991 Gulf War experience chronic and multi-symptom illnesses that have been collectively termed “Gulf War Illness”. Symptoms include fatigue, musculoskeletal changes, gastrointestinal symptoms and respiratory difficulty, as well as neurological symptoms such as mood and cognitive changes, depression and anxiety. The exact cause of these symptoms is still unknown, however, research suggests that exposure to multiple toxins in the course of military service and deployment to the Persian Gulf may be a contributing factor. Uniquely, these service members were given prophylactic dosing of the acetylcholinesterase inhibitor, pyridostigmine bromide (PB), to protect against the possibility of a nerve gas attack. Additionally, service members were exposed to significant quantities of insecticides, both through personal use of DEET-based repellants and through environmental exposure to organophosphates, such as chlorpyrifos (CPF). We’ve developed a mouse model of Gulf War Illness that recapitulates the multidimensional toxin exposure of Gulf War veterans. Mice were exposed to subcutaneous administration of PB, DEET and CPF over the course of two weeks. Following exposure, mice underwent testing to assess behavioral effects and brains were harvested to evaluate biochemical changes caused by Gulf War insults. In mice receiving toxin exposure, we found a significant increase in overall distance traveled and mean speed in an open field test when compared to vehicle controls. We also saw an increase in the amount of time spent and distance traveled in the perimeter of the arena near the walls as opposed to the center. This suggests that exposure to the toxins may be resulting in hyperactive, anxiety-like behavior in our mouse model, similar to that which is seen in veterans with Gulf War Illness. Our biochemical observations indicate that toxin exposure alters neurodegenerative factors. We hope to identify neurodegenerative mechanisms involved and define signaling pathways that could be modulated to reduce continuing chronic problems in this Veteran population.

Disclosures: B.A. Citron: None. **D.C. Driscoll:** None. **W.A. Ratliff:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.12/JJ28

Topic: H.02. Human Cognition and Behavior

Support: CDMRP GWI consortium award (GW 120037)

Title: Brain immune interactions in Gulf War Illness: Cytokines and cognition in US military veterans

Authors: *P. A. JANULEWICZ LLOYD[1], *P. A. JANULEWICZ LLOYD[1], T. HEEREN[2], E. SISSON[3], J. CIRILLO[1], M. KRENGEL[4], F. COLLADO[6], Z. BARNES[7], R. TOOMEY[5], R. J. KILLIANY[8], C. CHAISSON[3], L. STEELE[9], N. KLIMAS[7,6,10], K. AENNLE[7], M. ABREU[7], K.

SULLIVAN[1]
[1]Envrn. Hlth., [2]Biostatistics, [3]Data Coordinating Ctr., Boston Univ. Sch. of Publ. Hlth., Boston, MA; [4]Neurol., [5]Psychology, Boston Univ., Boston, MA; [6]Miami VA Hosp., Miami, FL; [7]Nova Southeastern Med. Campus, Ft. Lauderdale, FL; [8]Anatomy/Neurobio, Boston Univ. Sch. Of Med., Boston, MA; [9]Baylor Col. of Med., Houston, TX; [10]Col. of Osteo. Med., Miami, FL

Abstract: Background: Identifying objective biomarkers for persistent symptoms in ill US Gulf War (GW) veterans with GW Illness (GWI) has been the main focus at the Boston Gulf War Illness Consortium (GWIC). Symptoms of GWI include fatigue, pain and cognitive problems. Our prior studies showed cognitive decrements in veterans with GWI compared with healthy veterans.
Objectives: The aim of this study was to compare cognitive decrements and proinflammatory cytokine biomarkers in healthy versus ill GW veterans. Using an extensive cognitive battery that examined multiple domains of function including; attention/executive, memory, visuospatial and motor functions, we compared plasma cytokine biomarkers in ill versus healthy GW-deployed veterans. Sixteen cytokines were compared between the two groups.
Methods: Participants included 88 GW veterans, 70 with GWI and 18 healthy controls. Cases and controls did not differ by age, sex or education. The study population had a mean age of 52 years and 15 years of education. Cytokines were evaluated by a high sensitivity chemiluminescent multiplex ELISA assay.
Results: Ill GW veterans had significantly different levels of IL1b, IL2, IL17 and IL23 ($p<.05$) than the healthy control veterans. In addition, IL2 correlated with composite attention, visuospatial and memory domain scores and with individual subtests including visuoconstruction (Block Design), executive function (TMT Part B, Delis Kaplan Executive Function Scale, color-word naming subtest), and acquisition and retention of a complex figure (ROCFT immediate and delayed recall). Continuous performance (CPT3) mean reaction time was significantly correlated with IL6 ($p<.05$) and IL15 was significantly correlated with visuoconstruction and visual memory (Block Design and ROCFT delayed recall, in GWI cases).
Conclusions: This study is the first to report plasma cytokine biomarker differences and reduced performance on tasks of information processing speed, sustained attention, visuospatial and memory functioning in veterans with GWI. Further study of brain-immune interactions and cognitive outcomes should be conducted in larger cohorts to further validate these cognitive-immune biomarker findings in GWI.

Disclosures: P.A. Janulewicz Lloyd: None. **T. Heeren:** None. **E. Sisson:** None. **J. Cirillo:** None. **M. Krengel:** None. **F. Collado:** None. **Z. Barnes:** None. **R. Toomey:** None. **R.J. Killiany:** None. **C. Chaisson:** None. **L. Steele:** None. **N. Klimas:** None. **K. Aennle:** None. **M. Abreu:** None. **K. Sullivan:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.13/JJ29

Topic: B.05. Transporters

Support: US Army Medical Research Acquisition Activity

Title: Investigating increased glutamate transporter EAAT2 function as a potential therapeutic approach for Gulf War illness

Authors: *X. WANG[1], J. B. FOSTER[1], S. XU[1], K. HODGETTS[2], C.-L. G. LIN[1]
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Abstract: Gulf War illness (GWI) is a chronic disorder with central nervous system (CNS) impairments, such as mood deficits and cognitive difficulties. Several recent studies have demonstrated that excitotoxic damage caused by excess extracellular glutamate levels may play an important role in the pathophysiology of GWI. However, the underlying mechanisms linking the glutamatergic system dysfunction and the pathological changes in GWI remain unclear. Excitatory amino acid transporter 2 (EAAT2) is localized primarily in the peri-synaptic processes of astrocytes and is responsible for 80-90% of all glutamate transport in the CNS. EAAT2 plays a critical role in the homeostatic regulation of extracellular glutamate levels. In this study, we investigated whether increasing EAAT2 expression by LDN/OSU-215111, a small-molecule that can enhance EAAT2 translation, could normalize the dyshomeostasis of the glutamatergic system and consequently improve mood and cognitive functions in a mouse model of GWI. To mimic the neurotoxicant exposure and stress encountered by veterans during the GW, 3-4 month old C57BL6 mice were exposed to both GWI-related chemicals, including pyridostigmine bromide (PB), permethrin (PER), and N,N-diethyl-meta-toluamide (DEET), and chronic unpredictable stress for six weeks. During this period, the compound treated group received oral LDN/OSU-215111 everyday, while the control group received vehicle. Neurobehavioral studies were then conducted at 1-week, 1-month, and 3-month post-exposure to assess mood and cognitive functions. The following behavior tests were performed: open field, novelty suppressed feeding, sucrose preference, force swimming, tail suspension, Barnes maze and novel object recognition tests. After behavioral studies, mice were euthanized for pathological assessment. Synaptic integrity, astrocyte integrity, neuron loss, neurogenesis and glial activation were examined. Our current data indicates that compound treatment appears to have beneficial effects. The complete and detailed results will be presented.

Disclosures: X. Wang: None. **J.B. Foster:** None. **S. Xu:** None. **K. Hodgetts:** None. **C.G. Lin:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.14/JJ30

Topic: A.04. Transplantation and Regeneration

Support: Department of Defense (CDMRP Award W81XWH-14-1-0572 to AKS)

Title: Monosodium luminol improves cognitive, memory and mood function through modulation of oxidative stress, inflammation and neurogenesis in a model of gulf war illness

Authors: *A. K. SHETTY[1,2], B. SHUAI[1,2], S. ATTALURI[1], M. KODALI[1,2], G. SHETTY[1,2], B. HATTIANGADY[1,2], D. UPADHYA[1,2], A. BATES[1,2], X. RAO[1]
[1]Dept. of Mol. and Cell. Med., Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX; [2]Olin E. Teague Veterans' Med. Ctr., Temple, TX

Abstract: Cognitive, memory and mood impairments are among the most conspicuous symptoms of Gulf War Illness (GWI). Epidemiological studies imply that exposures to anti nerve gas agent pyridostigmine bromide (PB), pesticides and stress during the war caused GWI in a major fraction of Persian Gulf War-1 veterans. Our previous studies in a rat model have shown that exposures to GWI-related chemicals (GWIR-Cs) and mild stress for 4 weeks cause persistent cognitive, memory and mood impairments linked with increased oxidative stress, inflammation and waned neurogenesis in the hippocampus. Hence, drugs capable of suppressing oxidative stress and inflammation are of interest for reversing brain-related impairments in GWI. The drug monosodium luminol (MSL, BachPharma) is believed to exert robust antioxidant and anti-inflammatory properties through maintenance of redox homeostasis. We examined the efficacy of MSL to treat a rat model of GWI. Male SD rats were exposed daily to GWIR-Cs, DEET (60 mg/kg), permethrin (0.2 mg/kg), and PB (2 mg/kg), and 15-minutes of restraint stress for 4 weeks. Four months later, 3 cohorts of rats received daily MSL (40, 80 or 160 mg/Kg, oral) for 8 weeks while another group received vehicle (VEH). Behavioral tests performed in the last 3 weeks of MSL treatment revealed improved cognitive, memory and mood function in GWI-rats receiving higher doses of MSL (80 or 160 mg/Kg), in comparison to GWI rats receiving vehicle. This was evidenced through their ability to discern minor changes in the environment in an object location test, to explore a novel object over a familiar object in a novel object recognition test, to distinguish similar but identical experiences in a pattern separation test, to prefer sweet water in a sucrose preference test and their decreased latency to eat food in a novelty suppressed feeding test. Furthermore, the hippocampus of these animals displayed reduced concentration of malondialdehyde (a marker of lipid peroxidation), normalized expression of multiple genes related to oxidative stress, diminished inflammation (typified by reduced astrocyte hypertrophy and ED-1+ activated microglia), and increased neurogenesis with normalized neural stem cell

activity. Thus, daily intake of MSL at 80-160 mg/Kg doses can reverse cognitive, memory and mood impairments in GWI. In view of the role of oxidative stress and inflammation in impairing neurogenesis, cognitive, memory and mood function, it is likely that MSL-induced redox homeostasis suppressed inflammation, which in turn enhanced neurogenesis and improved cognitive, memory and mood function in this study.

Disclosures: A.K. Shetty: None. **B. Shuai:** None. **S. Attaluri:** None. **M. Kodali:** None. **G. Shetty:** None. **B. Hattiangady:** None. **D. Upadhya:** None. **A. Bates:** None. **X. Rao:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.15/KK1

Topic: H.01. Animal Cognition and Behavior

Support: R01 ES015382

DOD W81XWH-07-1-0618

Title: Two distinct compensatory activations underlying neuroplasticity for working memory deficits in veterans with Gulf War Illness and Chronic Fatigue Syndrome

Authors: *R. U. RAYHAN
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Abstract: Introduction: Solving a task requires multiple cortical regions involved in Working Memory (WM). WM refers to short term storage and processing of information. In addition to cortical regions, subcortical areas (i.e. the basal ganglia) are also required to facilitate cognition. Impairment of any links result in compensatory mechanisms seen in many neurodegenerative conditions such as Alzheimer's and Parkinson's. Active duty military personnel from the First Persian Gulf War developed chronic multisymptom complexes and severe neurological complaints. These overlapping disorders form Gulf War Illness (GWI). We used fMRI to provide the first ever objective evidence of two neurodegenerative phenotypes in GWI. **Methods:** Veterans were eligible if they were active military duty for at least 30 days from 1990-1991. 43 veterans (average age 50; 37 male) were included. There were also 10 Healthy Controls recruited to compare with the two pathological groupings. Healthy Controls recruited normal WM regions and did not have evidence of abnormal regions. Subjects had fMRI protocols during 2 modalities of the N-back paradigm (0-back and 2-back). Functional MRI data (BOLD) was acquired on a 3.0 T Siemens TIM Trio MRI scanner. Data was analyzed on SPM5 using a mixed-effects statistical analysis examining the brain activity for 2-Back>0-Back during the pre- and **N-Back Paradigm:** The N-Back task is a working memory paradigm that requires continual

encoding and retrieval of information. Stimuli are a series of randomly presented single letters (A, B, C, or D). The task was presented using a block design that alternated between 0-Back and 2-Back. For 0-Back, participants pressed the button corresponding to the letter presented. This block functioned as the control condition, as it does not require working memory or information manipulation. In contrast, the 2-Back required pressing the button corresponding to the letter presented 2 letters earlier. This condition does require working memory to continuously monitor and update information. **Conclusions:** Findings show both groups scored similarly on both the 0-back and 2 back paradigm but had to recruit different areas and networks to complete the tasks. GWI Group 1 suffers from dysfunctional Basal Ganglia circuits and recruit novel cerebellar areas to complete the N-back paradigm. GWI Group 2 has normal basal ganglia circuitry but have intrusion of default regions during the task implicating slower processing speed and inefficient use of task related areas. This is why neuropsychological testing has been inconclusive because active neuroplasticity has masked the clinical cognitive deficits .

Disclosures: R.U. Rayhan: None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.16/KK2

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: VACO SDIR

Title: Brain function in Gulf War Illness (GWI) and associated mental health comorbidities

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Abstract: Gulf War Illness (GWI) has affected a substantial number of Gulf War veterans. In addition, diagnosable mental health disorders frequently co-occur. Here we investigated synchronous resting-state brain activity patterns in GWI veterans with and without mental health disorders. Our goal was to characterize resting-state neural network activity as it relates to 3 prominent GWI symptoms (Fatigue, Pain and Neurological-Cognitive-Mood [NCM]) and symptoms of posttraumatic stress disorder (PTSD). Veterans completed self-report measures of GWI and PTSD symptoms as well as diagnostic interviews to evaluate MH conditions, resulting in two groups: GWI (N=40) and GWI+MH (N=65). Participants also underwent a MEG scan and Synchronous Neural Interactions (SNI) were computed. Within each group, linear regressions

were used to evaluate the effect of GWI (3 symptom domains, as above) and PTSD symptoms on SNI, with gender and age as covariates. Results demonstrated that neural representations of Fatigue, Pain, NCM, and PTSD symptom severity differed substantially within and across groups. These findings highlight distinctions at the neural level between symptom domains and suggest that GWI and GWI+MH reflect different brain networks.

Disclosures: R. Johnson: None. **L. James:** None. **B.E. Engdahl:** None. **A.C. Leuthold:** None. **A.P. Georgopoulos:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.17/KK3

Topic: D.03. Somatosensation: Pain

Support: DoD Grant GWI150187

Title: A neuroimmune basis of chronic pain in a rat model of gulf war illness

Authors: M. J. LACAGNINA[1], T. FABISIAK[1], K. SULLIVAN[2], J. P. O'CALLAGHAN[3], L. R. WATKINS[4], *P. M. GRACE[1]
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Abstract: Over the past 3 decades, 25-30% of veterans from the 1990-1991 Gulf War have consistently reported numerous unexplained chronic health symptoms impacting their quality of life, which has been termed Gulf War Illness (GWI). Epidemiological studies have identified exposure to acetylcholinesterase inhibitors and the chronic stress of war as sensitizing conditions that may predispose Service Members to GWI through exaggerated or persistent neuroinflammation. While rodent models of GWI mimic many of the symptoms of GWI, there are almost no reports of musculoskeletal pain assessment—a major symptom. Given the well-established role of neuroinflammatory signaling in exacerbating nociceptive processing, we propose a “two-hit” hypothesis of chronic pain for GWI in which the experimental GWI model (hit 1) confers a heightened neuroinflammatory response to a second inflammatory challenge (hit 2), leading to nociceptive hypersensitivity. To test this hypothesis, adult male Sprague Dawley rats were exposed to an established model of GWI by delivering the stress-related glucocorticoid corticosterone (CORT) in the drinking water (400 μg/mL) for 7 days, followed by an injection of the sarin surrogate diisopropyl fluorophosphate (DFP; 1.5 mg/kg, s.c.) on day 7 (hit 1). One week later, rats received a single injection of acidic saline (pH=4) or normal saline (pH=7) into

the gastrocnemius muscle. We observed profound allodynia to von Frey filaments in rats exposed to both hits (GWI + acidic saline). Allodynia was attenuated by systemic administration of the TLR4 antagonist (+)-naltrexone, implicating neuroinflammatory mechanisms in the maintenance of musculoskeletal pain. Ongoing studies are characterizing the neuroinflammatory profile throughout the nociceptive neuraxis.

Disclosures: **M.J. Lacagnina:** None. **T. Fabisiak:** None. **K. Sullivan:** None. **J.P. O'Callaghan:** None. **L.R. Watkins:** None. **P.M. Grace:** None.

Poster

071. Gulf War Illness: Mechanisms, Diagnostics, and Potential Treatments

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 071.18/KK4

Topic: D.03. Somatosensation: Pain

Support: DoD W81XWH-14-1-0543

5T32EB13180

Title: Glial activation in Gulf War Illness: Preliminary investigation

Authors: *D. S. ALBRECHT[1], C. A. BERGAN[1], O. AKEJU[3], D. CLAUW[4], L. CONBOY[5], R. R. EDWARDS[6], M. KIM[2], Y. C. LEE[7], V. NAPADOW[2], E. PROTSENKO[2], K. SULLIVAN[8], M. L. LOGGIA[2]
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Abstract: Gulf War Illness (GWI) is a chronic disorder characterized by dynamic symptomatology, including joint/muscle pain, fatigue, and cognitive decrements. While the exact pathophysiology of GWI remains unknown, recent studies suggest a possible link between GWI and chronic central nervous system (CNS) neuroinflammation, particularly glial activation. Exposure to neurotoxicants and other harmful chemicals during the Gulf War (GW) has been suggested to trigger GWI symptoms, and could be a priming event for pathogenic glial activation. However, glial activation has not yet been demonstrated in veterans with GWI. Seven GW veterans meeting the Kansas diagnostic criteria for GWI, and 18 healthy controls (including 4 healthy GW veterans without GWI) received a 90 minute an integrated PET/MRI brain scan, using [^{11}C]PBR28, which binds to the glial marker 18kDa translocator protein (TSPO). MPRAGE MRI scans were acquired for attenuation correction and anatomical

localization/normalization. 60-90 minute SUV images, reconstructed for each subject, were transformed to MNI space and spatially smoothed. Since no group differences were observed in whole-brain SUV ($p = 0.67$), variability in global signal was corrected for by normalizing the SUV maps by average whole brain signal. To evaluate possible group differences in [^{11}C]PBR28 uptake, a voxelwise analysis was conducted in FSL FEAT, using age, sex, and *TSPO* genotype as regressors of no interest. Statistical significance for this preliminary investigation was set at $z > 2.3$, uncorrected.

Voxelwise analyses revealed several regions in which SUVR was higher in GWI veterans compared to healthy controls, including anterior and middle cingulate cortices, hypothalamus, primary somatosensory cortex (S1), dorsomedial prefrontal cortex, brainstem, precuneus, superior parietal lobule, and superior frontal gyrus. Several of these regions survived a more stringent statistical threshold ($z > 3.1$): cingulate cortices, S1, brainstem, superior parietal lobule, and frontal cortex.

If confirmed in a larger cohort and at a more stringent statistical threshold, these results will provide preliminary evidence of glial activation in veterans with GWI. These data are in line with previous neuroimaging and physiological studies in veterans with GWI demonstrating CNS abnormalities, such as reduced cingulate cortex volume and impaired hypothalamic-pituitary-adrenal axis function.

Disclosures: **D.S. Albrecht:** None. **C.A. Bergan:** None. **O. Akeju:** None. **D. Clauw:** None. **L. Conboy:** None. **R.R. Edwards:** None. **M. Kim:** None. **Y.C. Lee:** None. **V. Napadow:** None. **E. Protsenko:** None. **K. Sullivan:** None. **M.L. Loggia:** None.

Poster

072. Sleep: Molecular Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 072.01/KK5

Topic: F.08. Biological Rhythms and Sleep

Support: NSERC to MBS

CIFAR to MBS

Title: Regulatory microRNAs associated with the *Drosophila* foraging gene at the intersection of sleep, stress and cognitive function

Authors: *S. D. BIERGANS[1], M. D. WARREN[2], Z. XIAO[1], H. E. SOREQ[3], M. B. SOKOLOWSKI[1,4]

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Jerusalem, Israel; [4]Child and Brain Develop. Program, Canadian Inst. of Advanced Res. (CIFAR), Toronto, ON, Canada

Abstract: Sleep is a complex behaviour that affects memory formation and is influenced by stress. The interplay between sleep, memory formation and environmental context requires multifaceted molecular regulation. This is because this interplay involves many different genes and molecular pathways, both shared by and unique to each behaviour and environmental context. MicroRNAs are excellent candidates for the regulation of interrelated complex behaviours since they can simultaneously repress the expression of many genes. However, how microRNAs actually affect complex behaviours and how they are modified by the environmental context remains unknown. The fruit fly, *Drosophila melanogaster*, is an ideal model for studying the interplay between sleep, memory and stress. Many of the brain regions and genes important to sleep and memory formation are well understood in flies and transgenic manipulations can be used to investigate gene regulation in a temporally and spatially precise way. We use the *foraging* gene which encodes a cGMP dependent protein kinase as a candidate gene for studying the roles of microRNAs in complex behaviours. The rover and sitter allelic variants of the *foraging* gene differ in their patterns of sleep, memory and stress resilience. *foraging*'s significant pleiotropy implies that its expression may be under intense scrutiny by regulatory mechanisms. We predicted that microRNA-932 targets *foraging* along with other genes crucial for sleep and memory formation using a microRNA target gene prediction tool. Interestingly, sitters show several SNPs in the intronic originated neuroligin-targeting microRNA-932 gene, suggesting potential differences in microRNA-932 expression between rovers and sitters. We first confirmed previous reports that rovers and sitters sleep differently using video recordings and tracking of individual flies. Sitters sleep less during the night and have an increased latency to sleep after lights off. The sleep behaviour of microRNA-932 KO flies largely phenocopies sitter sleep, but strongly differs from that of rover. We will move on to confirm the direct targeting of *foraging* by microRNA-932 using Luciferase assays and investigate whether microRNA-932 contributes to the increased resilience of rovers to stress along with the interaction of sleep and memory formation. Our study expands the understanding of the significance of regulatory networks in complex behaviours, and how they can be disrupted by detrimental environmental input.

Disclosures: S.D. Biergans: None. **M.D. Warren:** None. **Z. Xiao:** None. **H.E. Soreq:** None. **M.B. Sokolowski:** None.

Poster

072. Sleep: Molecular Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 072.02/KK6

Topic: F.08. Biological Rhythms and Sleep

Title: Increased expression of brain-enriched microRNA in sleep deprived mice hippocampus after treatment with melatonin

Authors: *A. HINOJOSA GODINEZ[1], M. QUIROGA ESPARZA[2], M. RUIZ MACIAS[2], A. GÁLVEZ CONTRERAS[2], M. FLORES SOTO[3], M. LUQUIN DE ANDA[2], R. E. GONZALEZ-CASTAÑEDA[4]
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Abstract: This study was designed to assess the effects of melatonin in brain-enriched microRNAs expression on sleep-deprived mice. To achieve this goal we used 40 Balb/c mice, which were sleep deprived using the flower-pot method for 96hrs and treated with melatonin (10mg/kg/day) during sleep deprivation. Selected MicroRNAs involved in hippocampal neurogenesis and neural maturation (mir-124-1, mir-9) were measured with qPCR from hippocampal extracts. We found that expression of all microRNAs (mir-124-1, $p<0.001$; mir-9, $p<0.05$) was significantly higher in melatonin treated and sleep-deprived group versus controls and this difference was found at day 21 after sleep deprivation. This evidence suggests that melatonin administration modifies molecular mechanisms involved in late neurogenesis and neural stem cell differentiation.

Disclosures: A. Hinojosa Godinez: None. **M. Quiroga Esparza:** None. **M. Ruiz Macias:** None. **A. Gálvez Contreras:** None. **M. Flores Soto:** None. **M. Luquin de Anda:** None. **R.E. Gonzalez-Castañeda:** None.

Poster

072. Sleep: Molecular Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 072.03/KK7

Topic: F.08. Biological Rhythms and Sleep

Support: DP2 OD017661

Title: Effects of network oscillations on mRNA translation in the hippocampus

Authors: *J. DELORME[1,2], V. KODOTH[1], S. ATON[2]
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Abstract: In the hours immediately following learning, new memories are labile and can be easily disrupted. Sleep deprivation is a reliable method for disrupting the consolidation of some forms of long-term memory. Since long-term memory formation is reliant on de novo protein

synthesis, we hypothesize that sleep stabilizes long-term memory by influencing protein synthesis. To test this hypothesis, we characterized the phosphorylation state of the ribosomal S6 protein (rpS6) in the mouse hippocampus as a function of both learning and sleep. We find that 3 hours of sleep deprivation selectively reduces phosphorylation of rpS6 at sites 244-247, but not sites 235-236 in the cell bodies of hippocampal area CA1, CA3, and dentate gyrus (DG) neurons. Furthermore, while we observed no differences in the phosphorylation state of rpS6 244-247 30-mins or 3hrs associated with contextual fear conditioning in the hippocampus. Intriguingly, if animals were sleep deprived for 3hrs following CFC, we observed selective reductions in rpS6 phosphorylation in the CA1 and DG subregions after conditioning. Because recent studies have suggested that phosphorylating these residues can influence translation rates, we speculated that these changes may reflect changes in the rate of protein synthesis in the hippocampus as a function of sleep in the hours following learning.

Disclosures: J. Delorme: None. **V. Kodoth:** None. **S. Aton:** None.

Poster

072. Sleep: Molecular Mechanisms

Location: Halls A-C

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Topic: F.08. Biological Rhythms and Sleep

Support: US Veterans Administration

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The content of this work does not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Title: A fate-mapping approach to trace the developmental origin of forebrain GABAergic neurons controlling sleep and wakefulness

Authors: *R. E. BROWN[1], C. YANG[2], J. T. MCKENNA[2], J. M. MCNALLY[2], M. ANDERSON-CHERNISOFF[2], S. WINSTON[2]
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Abstract: Cortically-projecting GABAergic neurons located in the basal forebrain (BF) play important roles in promoting wakefulness and cortical activation. Other GABAergic neurons in hypothalamic regions neighboring the BF promote sleep or circadian rhythms. This raises the question: how are GABAergic neurons with distinct roles in the control of sleep-wake behavior generated? To begin to answer this question, here we investigate the developmental origin of these neurons using a fate-mapping approach. Mice with Cre Recombinase expression driven by the promoter region of a transcription factor, Lim homeobox 6 (Lhx6), which is selectively expressed in forebrain GABAergic neurons derived from the medial ganglionic eminence (MGE) were purchased from Jackson Laboratories (Bar Harbor, ME). A cross with a Cre-reporter strain expressing the red fluorescent protein, tdTomato, was used to investigate the location of MGE-derived neurons. Immunostaining was used to identify the subclass of GABAergic neurons. Adeno-associated viral vectors expressing excitatory receptors (hM3Dq) activated exclusively by the designer drug, clozapine-N-oxide (CNO), were injected bilaterally into BF to test the effect on sleep-wake states. Neurons specified by Lhx6 were widely distributed throughout the BF and the cortex but were largely absent in sleep-promoting areas of the preoptic hypothalamus and the master circadian pacemaker, the suprachiasmatic nucleus. BF neurons labeled with tdTomato included parvalbumin-containing projection neurons involved in promotion of wakefulness and cortical gamma-band oscillations. Approximately half of the PV neurons counted in the BF of one Lhx6-Cre-tdTomato mouse contained tdTomato. However, only 13.7 % of tdTomato neurons were PV+, suggesting that Lhx6 also specifies other types of BF GABA neurons. Chemogenetic activation of Lhx6-derived BF neurons strongly increased wakefulness and gamma band power for >1 hr after i.p. injection of CNO (0.3 mg/kg) at ZT2. CNO treated mice had 83±3 % wakefulness whereas saline-treated mice had only 30±1 % (n=2) in the period 20-80 min following injection. Saline-injected mice also had increased wakefulness but only in the 20 min immediately following the injection. Our results suggest that wakefulness-promoting BF GABAergic neurons but not GABAergic neurons which promote sleep or circadian rhythms are derived from MGE progenitor cells expressing Lhx6. Cortical interneurons implicated in schizophrenia and other neurodevelopmental disorders are derived from the same pathway suggesting a potential involvement of BF Lhx6-derived neurons in the sleep-wake disturbances observed in these disorders.

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Poster

072. Sleep: Molecular Mechanisms

Location: Halls A-C

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Program#/Poster#: 072.05/KK9

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 1K01AG041520

NIH Grant 1R01NS096151

NIH Grant 1R21NS101469

Title: Mch neurons are neither gabaergic nor glutamatergic in lateral hypothalamus of mice

Authors: C. BLANCO-CENTURION[1], E. BENDELL[1], B. ZOU[1], A. VIDAL-ORTIZ[1], P. J. SHIROMANI[1,2], *M. LIU[1]
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Abstract: There is an inconsistency on whether MCH neurons in lateral hypothalamus contain GABA or glutamate. To resolve this debate, we bred two transgenic mice models: VGAT/EYFP mice expressing EYFP in GABA neurons by crossing R26R-EYFP mice (stock #006148) and Vgat-ires-Cre knock-in mice (stock #016962); and VGLU/tdTomato mice expressing tdTomato in glutamate neurons by crossing Vglut2-ires-Cre knock-in mice (stock #016963) with Ai14 mice (stock #007914). Hypothalamus sections from these mice were processed for orexin and Melanin-concentrating hormone (MCH) immunofluorescent staining. Co-localization was determined using 3D computer reconstructions of Z stacks with an optical section of 1 micron. Results showed that MCH neurons are neither VGAT positive nor VGLUT2 positive; 86% of orexin neurons are VGLU2 positive while none are VGAT positive. No co-localization was found between MCH and orexin. These results demonstrated that MCH, orexin and GABAergic neurons are distinct cell groups in lateral hypothalamus. MCH neurons are neither GABAergic nor glutamatergic while most of orexin neurons are glutamatergic. These results indicated that MCH neurons might promote sleep solely by MCH signaling while orexin neurons might use both orexin and glutamate signaling to promote arousal.

Disclosures: C. Blanco-Centurion: None. **E. Bendell:** None. **B. Zou:** None. **A. Vidal-Ortiz:** None. **P.J. Shiromani:** None. **M. Liu:** None.

Poster

072. Sleep: Molecular Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Support: R01NS091126

P01HL095491

Title: Orexin mediates feed-forward inhibition of VLPO sleep-active neurons - a mechanism for controlling arousal

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Abstract: The ventrolateral preoptic area (VLPO) plays an essential role in the initiation and maintenance of sleep. It contains a cluster of sleep-active neurons that are GABAergic and co-expresses galanin ($VLPO^{GABA/Gal}$). VLPO is innervated by wake-promoting neurons and the $VLPO^{GABA/Gal}$ neurons are strongly inhibited by noradrenaline, carbachol and serotonin. VLPO also receives input from orexin neurons and administration of orexin in VLPO arouses mice from sleep, suggesting that orexin might be inhibiting the sleep-active $VLPO^{GABA/Gal}$ neurons. However, orexin is an excitatory peptide, thus orexin's effect in the VLPO remains unclear. In this study we investigate the effect of orexin on VLPO neurons in brain slices. We recorded VLPO neurons in brain slices from WT and V*gat-IRES-cre* mice. We filled the recorded cells with biocytin for anatomical localization. We recorded from VLPO GFP- and Tdtomato-labelled GABAergic neurons in *Vgat-IRES-cre* mice that were both injected in VLPO with an AAV-*flex*-GFP and AAV-*flex*-Tdtomato. We identify VLPO-sleep active neurons based on the inhibitory responses to noradrenaline or carbachol and/or by the presence of VGAT and galanin mRNAs using single cell RT-PCR. We found a dual response to orexin in VLPO. About 54% of VLPO neurons were excited by orexin but 46% were inhibited. Orexin-mediated inhibition of VLPO neurons was completely abolished by the GABAA antagonist bicuculline indicating that orexin inhibits VLPO neurons through release of GABA. Furthermore, we found that the VLPO neurons that were inhibited by orexin were also inhibited by carbachol or noradrenaline suggesting that they could be the $VLPO^{GABA/Gal}$ sleep-active neurons. We tested this hypothesis by recording VLPO GABAergic neurons. Orexin increased the frequency of spontaneous IPSCs in 50% of the VLPO GABAergic neurons and these neurons expressed galanin mRNA. This confirms that orexin inhibits $VLPO^{GABA/Gal}$ sleep-active neuron by increasing GABAergic afferent input. This GABAergic input could originate from the local neurons that are directly activated by orexin. We propose that during wakefulness $VLPO^{GABA/Gal}$ sleep-active neurons are strongly and directly inhibited by wake-promoting signals, such as noradrenaline, carbachol and

serotonin. Whereas, orexin could act by activating local GABAergic neurons that in turn produce feed-forward inhibition of $VLPO^{GABA/Gal}$ sleep-promoting neurons.

Disclosures: **R. De Luca:** None. **D. Park:** None. **S. Bandaru:** None. **E. Arrigoni:** None.

Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: DFG SFB TR-654

Title: Cortical circuit activity underlying slow oscillations and spindles

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Abstract: Slow oscillations (SOs) and sleep spindles are hallmarks of the EEG during slow wave sleep (SWS). Both oscillatory events, especially when co-occurring in the constellation of spindles nesting in the SO-upstate, are considered to support memory formation and underlying synaptic plasticity. The regulatory mechanisms of this function at the circuit level are poorly understood. Here we used, in combination with EEG recordings, two-photon imaging in mice to record calcium activity from cortical pyramidal (Pyr) cells and neighboring parvalbumin positive (PV-In) or somatostatin positive interneurons (SOM-In) during sleep, representing the main contributors to the cortical excitatory/inhibitory balance. As expected, excitatory Pyr cells activity was increased during the upstate of solitary SOs. A similar increase in Pyr activity was only marginal during spindles, whereas maximum excitatory Pyr activity was found when spindles co-occurred with the SO up-state. The beginning of the downstate as well as the beginning of the up-state of solitary SOs was accompanied by distinctly enhanced activity of inhibitory SOM-In, whereas during spindles activity of PV-In increased, with this increase in inhibitory PV-In activity being particularly pronounced when spindles nested in the SO upstate. Both spindles and SOs were followed by a general decrease in activity persisting over several tens of seconds for Pyr and SOM-In. Additional wide-field calcium imaging of Pyr confirmed for the SO a more wide spread topography than spindles as well as an anterior-to-posterior travelling of the SO. Our data indicate that spindles occurring during SO upstates are characterized by a particularly strong somatic inhibition of Pyr via PV-In in the absence of strong dendritic inhibition via SOM-in. These conditions might optimize synaptic plasticity within local cortical circuits.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH F32NS098615

Title: Noradrenergic transmission in the ventral periaqueductal gray modulates arousal

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Abstract: The locus coeruleus (LC), the major noradrenergic nucleus in the brain, is classically considered a critical node in the arousal system. High LC neuron firing is associated with focused attention, goal-directed behavior, stress responses, and wakefulness. By contrast, lower LC activity drives distractibility and behavioral flexibility, with these neurons mostly quiescent during sleep. However, the specific LC projections that modulate arousal are not fully known. An understudied population of dopamine neurons in the ventral periaqueductal gray (vPAG) is active during wake and inactive during sleep, and previous research has shown that the LC projects to the ventral periaqueductal gray, making it an ideal candidate to modulate arousal. Consistent with the hypothesis of an LC-vPAG arousal circuit, we found that activation of α1-adrenergic receptors (α1ARs) increased the activity of vPAG dopamine neurons, and direct activation of vPAG dopamine neurons using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and the DREADD ligand clozapine-N-oxide (CNO) promoted wakefulness. Additionally, blockade of α1ARs in the vPAG decreased arousal, and agonism of vPAG α1ARs promoted wakefulness and rescued the sleepy phenotype of mice lacking norepinephrine. Immuno-electron microscopy revealed that a surprisingly large proportion of α1ARs in the vPAG are located on astrocytes. Because vPAG astrocytes contain α1ARs, and α1ARs are coupled to Gq, we used the hM3Dq DREADD to test whether Gq-induced activation of vPAG astrocytes could promote wakefulness. Indeed, intra-vPAG infusion of CNO promoted wakefulness in GFAP-hM3Dq transgenic mice that express Gq DREADDs exclusively in astrocytes. Together, these results support the hypothesis that noradrenergic transmission at astrocytic α1ARs in the vPAG promotes arousal by activating local wake-promoting dopamine neurons.

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Poster

072. Sleep: Molecular Mechanisms

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Title: Increased sleep and spindle activity in mGluR5 knockout mice

Authors: *D. D. AGUILAR[1], S. THANKACHAN[2], R. E. STRECKER[2], R. BASHEER[2], R. W. MCCARLEY[2], R. E. BROWN[2], J. M. MCNALLY[2]
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Abstract: The metabotropic glutamate receptor 5 (mGluR5) is a potential therapeutic target for schizophrenia (Sz) due to its expression in parvalbumin-containing neurons and facilitation of NMDA receptor function. Supporting this idea, positive allosteric modulators (PAMs) of the mGluR5 alleviate various Sz-like phenotypes in animal models. Here, we examined this receptor's involvement in gamma band oscillations (GBO) using mGluR5 KO mice. We hypothesized a Sz-like impairment in both spontaneous and evoked GBO. Furthermore, we predicted that mGluR5 PAMs would inhibit NMDA antagonist-evoked gamma oscillations. Since the mGluR5 plays a role in thalamic reticular nucleus (TRN) processing (Sun et al 2016 *J Neuro*) it may act on sleep spindle generation. Previously, mGluR5 knockout (KO) mice have demonstrated increased non-rapid eye movement sleep (NREM) (Ahnaou et al 2015 *Behav Brain Res*). We thus examined both sleep/wake and sleep spindle activity of mGluR5 KO mice. We hypothesized mGluR5 KO mice would demonstrate increases in NREM sleep and sleep spindle density.
Adult male and female wild type C57BL/6 and mGluR5 KO mice were used for *in vivo* EEG/EMG recordings. EEG electrodes were stereotaxically implanted bilaterally above the

frontal cortices and EMG electrodes placed in the nuchal muscle. Ketamine (5mg/kg i.p.) or MK-801 (0.1mg/kg i.p.) evoked GBO power was recorded from WT mice pretreated with an mGluR5 PAM (CDPPB or VU040551, each 30mg/kg i.p.) or vehicle [10% Tween 80 or 20% (2-hydroxypropyl)-β-cyclo-dextrin]. After 48 hours of tethered habituation, analysis of sleep/wake states and algorithmically detected spindles was performed over 24 hours. To examine evoked GBO we measured the auditory steady state response (ASSR) in both cohorts over a frequency range of 20-60Hz (90 dB click train).
Pretreatment with an mGluR5 PAM did not block NMDAR antagonist-evoked increases in GBO power (n=5-8 per group). Compared with controls, mGluR5 KO mice showed decreased time spent in wakefulness and increased time spent in NREM sleep over light and dark phases (n = 4 per group). Knockout mice had more NREM spindles (Avg spindles: KO 3906 ± 137, WT 3016 ± 185), as well as decreased theta power and increased GBO power during REM sleep compared with controls. In the ASSR, a 20 Hz audio stimulus evoked an increase in 20Hz cortical power for WT (n=4) but not mGluR5 KO mice (n=3).
In conclusion, our preliminary data confirm mGluR5 KO mice spend increased time in NREM sleep, replicating previous work. Novel findings included decreased wakefulness during the light phase and increased spindles in mGluR5 KO mice. Knockouts showed an impaired ability of the ASSR to increase 20Hz power.

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Poster

072. Sleep: Molecular Mechanisms

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Program#/Poster#: 072.10/KK14

Topic: F.08. Biological Rhythms and Sleep

Support: MH59839

Title: The effects of BDNF on local EEG patterns and behavioral testing

Authors: *P. A. GEIST[1], A. BARNES[2], B. N. DULKA[3], M. TOTTY[3], S. DATTA[4]
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Abstract: Brain derived neurotrophic factor (BDNF) is critical in regulating neuronal plasticity, particularly that of learning and memory. Cortical and hippocampal EEG spectral power has also been shown to influence learning and memory. In this study, we investigated the effects of globally reduced BDNF levels on learning and EEG power using BDNF heterozygous (+/-) rats. To do this, we employed several behavioral tests that depend on cortical and hippocampal

plasticity to varying degrees: novel object recognition, which is theorized to rely on several cognitive systems; contextual fear, which is highly hippocampal-dependent; and cued fear, which has been shown to be amygdala-dependent. In addition, we examined the effects of global BDNF reduction on cortical and hippocampal EEG spectral power using chronically implanted electrodes in both the motor cortex and dorsal hippocampus. Interestingly, our results revealed sex-dependent effects in each of our tests. Our behavioral tests revealed that male BDNF +/- rats were impaired in novelty recognition, while females exhibited deficits in cued fear retention. Both sexes exhibited impairments in contextual retention. Results from the EEG spectral power experiments showed that male BDNF +/- rats displayed a decrease in cortical theta power, but female BDNF +/- rats exhibited no change from wild types. In addition to these findings, we found hippocampal EEG spectral power decreases in low frequencies and increases in high frequencies for both sexes, but only males display a significant difference from wild type controls. Given the theorized role of BDNF in learning and memory plasticity, these results suggest that BDNF drives both cognitive plasticity and regulates oscillatory firing patterns. Critically, BDNF potentially represents a mechanistic link between these processes. Importantly, the disparity between rats of different sexes suggests that males may be more sensitive to disturbances in BDNF levels than females. This could be related to the mechanism of learning differing between sexes, and may have clinical applications in the treatment of learning and memory disorders.

Disclosures: **P.A. Geist:** None. **A. Barnes:** None. **B.N. Dulka:** None. **M. Totty:** None. **S. Datta:** None.

Poster

072. Sleep: Molecular Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Support: MH59839

Title: The role of sleep-dependent neuronal network synchronization in fear memory consolidation

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Abstract: Sleep plays an important role in memory consolidation through the facilitation of neuronal plasticity; however, the mechanism underlying this process remains elusive. It has previously been demonstrated that neural oscillations are an intrinsic mechanism by which the brain precisely controls neural ensembles. Inter-regional synchronization of these oscillations is

also known to facilitate long-range communication and long-term potentiation (LTP). In the present study, we investigated how the characteristic rhythms found in local field potentials (LFPs) during non-REM and REM sleep play a role in memory consolidation. Chronically implanted bipolar electrodes in the lateral amygdala (LA), dorsal and ventral hippocampus (DH, VH), and the infralimbic (IL) and prelimbic (PL) prefrontal cortex were used to record LFPs across sleep-wake activity following each day of a Pavlovian cued fear conditioning paradigm. Analysis of baseline phase-locking value (PLV) revealed that REM sleep theta rhythms are the most synchronous, lasting neural oscillation in the cortico-limbic system. This measure of connectivity contrasts to existing literature suggesting REM sleep is a disentangled state. Interestingly, many changes in neural oscillatory synchronization observed during non-REM and REM sleep were also counter-intuitive based on existing literature that suggests bidirectional roles for the IL and PL. Furthermore, we show here for the first time that the mean phase difference between the LA and VH within subjects predicts individual changes in freezing following fear extinction. This suggests that the role of REM sleep theta rhythms in memory consolidation may rely more on the relative phase-shift between neural oscillations, rather than the extent of phase synchronization. Collectively, these results provide a novel perspective on the role of neuronal rhythms found during sleep in emotional memory consolidation. This study highlights the importance of a better understanding of neuronal network dynamics in order to completely elucidate sleep's role in behavioral plasticity.

Disclosures: **M. Totty:** None. **L. Chesney:** None. **P.A. Geist:** None. **S. Datta:** None.

Poster

072. Sleep: Molecular Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Support: MH59839

Title: A novel role of BDNF in the regulation of REM sleep

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Abstract: Brain derived neurotropic factor (BDNF) is a widely expressed neurotropin with various functions involving neurogenesis, behavioral plasticity, and emotional processing. Based on our recent pharmacological studies on adult male SD rats we hypothesized that BDNF is involved in the homeostatic regulation of REM sleep. To test this hypothesis, adult male and female SD wild-type (WT) and heterozygous BDNF knockdown (KD) rats were chronically

implanted with sleep-wake (S-W) recording electrodes. After surgical recovery and adaptation recording sessions, we examined genotype and sex differences in spontaneous S-W activity. The results of this study revealed significant genotype differences but no sex differences in the spontaneously occurring S-W activity. We found that, compared to the WT rats, the KD rats had fewer REM sleep episodes and spent significantly less time in REM sleep. Next, to determine the effects of genotype in homeostatic regulation of REM sleep, rats were subjected to a 3h period of selective REM sleep deprivation protocol. The results of this deprivation study showed that selective REM sleep deprivation induced a strong homeostatic drive for REM sleep in the WT rats but not in the KD rats. Additionally, KD rats failed to exhibited rebound REM sleep during the recovery S-W period. Collectively, these results, provide novel evidence that a normal level of BDNF is critical for spontaneously occurring REM sleep and also for the homeostatic regulation of REM sleep.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant MH59839

Title: Cellular and molecular mechanisms of REM sleep homeostatic drive: Links to neuronal and behavioral plasticity

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Abstract: REM sleep homeostatic drive (RSHD) plays a key role in behavioral plasticity, and deficits in RSHD are implicated in the development of many neuropsychiatric disorders. Additionally, expression levels of brain-derived neurotrophic factor (BDNF) in the REM sleep-promoting area, the pedunculopontine tegmentum (PPT), have been associated with RSHD. Although BDNF has long been associated with neuronal and behavioral plasticity, its role in RSHD remains poorly understood. Thus, we investigated whether PPT BDNF causes the development of RSHD through cellular processes similar to those involved in neuronal development and plasticity: TrkB activation and downstream extracellular signal-regulated kinase 1 and 2 (ERK1/2) activity. Our behavioral data indicate that freely moving rats subjected to a short period (3 hours) of selective REM sleep restriction (RSR) exhibited a strong RSHD. Molecular analyses revealed that this increased RSHD was strongly correlated with increased

phosphorylation of ERK1/2 and BDNF expression in the PPT. Pharmacological results demonstrated that the application of the TrkB inhibitors K252a and ANA-12 into the PPT suppressed BDNF expression and prevented RSHD. As expected, microinjections of the ERK1/2 activation inhibitor U0126 into the PPT produced similar results; U0126 prevented RSHD and suppressed PPT BDNF expression. These results, for the first time, provide direct evidence that the positive interaction between BDNF-TrkB signaling and ERK1/2 activity in the PPT is a causal factor for the development of RSHD. These findings provide a novel understanding of how specific RSHD-associated molecular changes can be related to neuronal plasticity and memory processing.

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Poster

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Topic: F.08. Biological Rhythms and Sleep

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CA199928

Title: Enhancement of synaptic plasticity by NYX-2925: Sleep cycle EEG studies in rats

Authors: *J. S. BURGDORF[1,3], K. LEADERBRAND[3], E. M. COLECHIO[3], C. J. OLKER[2], E. J. SONG[2], N. GHOREISHI-HAACK[3], A. L. GROSS[3], M. H. VITATERNA[2], F. W. TUREK[2], X. .-L. ZHANG[4], P. K. STANTON[4], T. M. MADSEN[3], M. A. KHAN[3], R. A. KROES[1,3], J. R. MOSKAL[1,3]
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Abstract: Aptinyx has developed a novel class of small molecule N-Methyl-D-Aspartate (NMDA) receptor modulators with broad applicability across neurologic and psychiatric disorders. NYX-2925 is orally bioavailable and currently entering a Phase II trial for neuropathic pain, a condition in which sleep disruption is a core symptom. NYX-2925 facilitates synaptic plasticity as measured by enhancement of long-term potentiation (LTP) both *in vitro* and *ex vivo* 1-7 days post-dosing (1-10 mg/kg, PO). NYX-2925 also enhances medial prefrontal cortex (MPFC)-dependent novel object recognition and positive emotional learning. The present studies examine the effects of NYX-2925 on activity-dependent long-term synaptic plasticity *in vivo* using 24 hr EEG recording from the MPFC in the presence or absence of sleep deprivation.

Sleep deprivation has been shown to suppress plasticity and decrease pain thresholds. NYX-2925 significantly facilitated slow wave sleep during the sleep (lights on) period, and this effect persisted for 3 days following a single dose. Although total REM was not affected, sleep bout duration and non-REM to REM transition times were increased, suggesting better sleep quality. Delta power during wake was decreased, suggesting less drowsiness. In contrast, the NMDAR antagonist ketamine acutely suppressed REM and non-REM sleep and increased delta power during wake. Ketamine also increased gamma power during wake, indicative of its dissociative effect. These data suggest that NYX-2925 could enhace synaptic plasticity via improved sleep quality as well as vigilance during wake. As such, the facilitation of slow wave sleep by NYX-2925 has the potential to both reduce symptoms of neuropathic pain and serve as a biomarker for drug efficacy.

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Poster

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Title: Myelin modifications after chronic sleep loss in adolescent mice

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Abstract: Previous studies have found that sleep loss can suppress the expression of genes implicated in myelination and can have adverse effects on oligodendrocyte precursors cells. Additionally, sleep may favor myelination by promoting the expression of genes involved in its formation and maintenance. It has also been shown that there is a critical period for myelination during adolescence, and that affecting myelination during this period can produce changes that persist into adulthood. These results suggest that sleep loss can have detrimental effects on the formation and maintenance of myelin, and if these effects occur during adolescence, that they may have long-term consequences for oligodendrocytes. We tested these hypotheses by evaluating ultrastructural modifications of myelin via scanning electron microscopy in two highly myelinated brain regions, the corpus callosum (CC) and lateral olfactory tract (LOT), of four week old male mice (B6.Cg-Tg(Thy1-YFP)16Jrs/J) exposed to different periods of sleep loss, from a few hours of sleep deprivation (SD; n=2) to ~5 days of chronic sleep restriction (CSR; n=3), and compared them against a control group, where no sleep deprivation occurred (S; n=4). After the 5-day sleep restriction, we allocated some of the CSR mice to a recovery sleep group (RS; n=3), where they slept *ad libitum* for 2 days. We measured g-ratio (the ratio of the diameter of the axon to the outer diameter of the myelinated fiber), axon diameter, and myelin thickness of thousands of axons (~1,500 axons per animal were measured). We find that the g-ratio increases after CSR in both the CC and LOT when compared to the sleep control group ($z = 2.964$, $p = 0.016$), and this effect is mediated by a reduction in myelin thickness ($z = 2.651$, $p = 0.0398$), especially for large axons ($z = 4.087$, $p = 0.0006$). After 2 days of recovery sleep, the g-ratio and myelin thickness renormalizes, and is not significantly different from the sleep group.

However, within the LOT, the number of myelinated axons is reduced ($z = 2.808$, $p = 0.025$). Together, these findings suggest that chronic sleep loss can negatively affect myelination during adolescence.

Disclosures: **J. Haswell:** None. **M. Bellesi:** None. **L. de Vivo:** None. **W. Marshall:** None. **G. Tononi:** None. **C. Cirelli:** None.

Poster

072. Sleep: Molecular Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 5UM1HL112856

Title: Dimethyl sulfoxide (DMSO) concentration affects the impact of dronabinol on sleep apneas in rats

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Abstract: Dimethyl sulfoxide (DMSO) commonly is used as a vehicle for water-insoluble lipophyllic substances. However, DMSO has its own biological and physiological effects, potentially confounding interpretation of findings. Therefore, minimizing the concentration of DMSO employed as a vehicle is appropriate. We previously demonstrated that dronabinol, a synthetic version of Δ9-THC that activates cannabinoid type 1 (CB_1) and/or type 2 (CB_2) receptors, dissolved in 100% DMSO decreased the frequency of spontaneous sleep-related central apnea and changed sleep architecture in Sprague-Dawley rats. It is unknown whether dronabinol would have similar effects if dissolved in a lower concentration of DMSO. Here, we examine the effects of dronabinol – dissolved in DMSO diluted in PBS to a concentration of 25% – on sleep apnea and sleep architecture. Adult male Sprague-Dawley rats were anesthetized and implanted with bilateral stainless steel screws into the frontal/parietal bones of the skull for EEG recording and bilateral wire electrodes into the nuchal muscles for EMG recording. The EEG/EMG leads were soldered to a miniature connector and fixed to the skull. Rats were allowed to recover from surgery for one week. Each animal was recorded by polysomnography on multiple occasions (10:00 to 16:00) separated by at least 3 days. The study was a fully nested, repeated measures crossover design, such that each rat received each of 8 intraperitoneal injections one time: vehicle alone (25% DMSO in PBS); vehicle and CB_1 antagonist (AM 251, 5 mg/kg); vehicle and CB_2 antagonist (AM 630, 5 mg/kg); vehicle and CB_1/CB_2 antagonist (5 mg/kg); dronabinol alone (10 mg/kg); dronabinol and CB_1 antagonist; dronabinol and CB_2 antagonist; dronabinol and CB_1/CB_2 antagonist. Our results showed that dronabinol in 25%

DMSO significantly (P<0.05) decreased REM sleep, replicating our previous finding with dronabinol in 100% DMSO. However, in contrast to our previous work where dronabinol in 100% DMSO decreased sleep apneas, dronabinol in 25% DMSO exerted no effect on the frequency of sleep apneas. Our results suggest that DMSO concentration impacts the physiological responses to dronabinol.

Disclosures: M.W. Calik: None. **D.W. Carley:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cortex Pharmaceuticals.

Poster

072. Sleep: Molecular Mechanisms

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Support: Uehara Memorial Foundation Research Fellowship

NIH Grant R01 MH087592

Title: Awakening actions of norepinephrine probed with cell type-specific CRISPR gene editing in locus coeruleus

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Abstract: The locus coeruleus is a small nucleus containing numerous norepinephrine (LC-NE) neurons in the brainstem and widely projects to diverse brain areas including hippocampus, amygdala and cerebral cortex. We previously showed an optogenetic stimulation of LC-NE neurons induces immediate arousal. However, the LC neurons also secrete other neurotransmitters such as dopamine in addition to NE. Thus, it is not yet clear whether the release of NE itself is essential for the arousing effects of LC-NE neurons. To address this problem, we used a cell type-specific CRISPR/Cas9 technology to disrupt the gene of dopamine beta hydroxylase (dbh), an enzyme necessary for NE synthesis, in LC-NE neurons. First, we constructed AAV vectors carrying non-targeting control single guide RNA or Dbh-targeting single guide RNA and then packaged them into the DJ serotype (AAV-DJ sgControl, AAV-DJ sgDbh). We next crossed Cre-inducible Cas9 knockin mice with noradrenergic-directed driver (Th-Cre) mice. We used Th-Cre /Cas9 double heterozygous mice for all following experiments. The LC injection of AAV-DJ sgDbh reduced Dbh immunoreactivity in Th-positive neurons by 85% compared to the contralateral injection of AAV-DJ sgControl. Using an ELISA assay, we also found that the amount of NE in the LC projection areas was significantly decreased in

sgDbh-infused but not in sgControl-infused mice. To examine the role of NE in regulating wakefulness, we measured the latency of sleep-to-wake transitions with optogenetic stimulation of dbh-disrupted LC using channelrhodopsin-2. Whereas optogenetic stimulation of sgControl-infused LC neurons induced immediate arousal, LC-specific Dbh disruption completely blocked it. Together, these results indicate that NE, not other neurotransmitters, arising from LC neurons are indispensable for LC-mediated regulation of wakefulness.

Disclosures: H. Yamaguchi: None. **L. de Lecea:** None.

Poster

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Topic: F.08. Biological Rhythms and Sleep

Support: Research Grant Program at Escuela de Medicina, Universidad Anáhuac Mayab

Title: AA-5-HT Blocks the wake-inducing properties of cannabidiol or modafinil during the lights-on period in rats

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Abstract: The endocannabinoid system exerts multiple and complex modulatory physiological functions. For instance, accumulative evidence has suggested that the endocannabinoid system modulates the sleep-wake cycle. Among the elements of the endocannabinoid system that seems to modulate sleep, the role of FAAH has been described. To understand the neurobiological properties of FAAH in sleep control, the use of inhibitors, such as URB597have been reported. However, the effects in sleep of injections of several FAAH inhibitors such as 1-heteroarylpropan-2-ones, piperidinyl thiazole isoxazoline, PF-04457845, JNJ-42165279, BIA 10-2474, AM3506, URB694, ARN146333-carboxamido-5-aryl-isoxazole, N-aryl 2-aryloxyacetamides, and AA-5-HT remain to be described. From previous experiments, we found that AA-5-HT promotes sleep if injected during the lights-off period of rats. If AA-5-HT is a sleep-promoting compound. We then investigated whether this drug would block the wake-inducing effects of cannabidiol (CD) or modafinil (MOD) during the lights-on period. Results showed that AA-5-HT caused no statistical difference in waking, slow wave sleep (SWS) or

rapid eye movement sleep (REMS) if administered during the lights-on period. Next, a single administration of CBD (30mg/Kg, ip) enhanced alertness and decreased SWS as well as REMS. Moreover, the injection of MOD (30mg/Kg, ip) increased waking (W) and decreased SWS as well as REMS. Importantly, administration of AA-5-HT 15 min before either CBD or MOD injection prevented the increase in alertness enhancement by these compounds. Our preliminary data suggested that AA-5-HT was able to block the wake-promoting effect caused by either CBD or MOD in rats during the lights-on period. Further studies are needed to explore the possibility that AA-5-HT could control insomnia-like behaviors.

Disclosures: M. Salas-Crisostomo: None. **N. Barbosa-Rocha:** None. **H. Budde:** None. **S. Machado:** None. **E. Murillo-Rodriguez:** None.

Poster

072. Sleep: Molecular Mechanisms

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MEXT Grant 16H01629

MEXT Grant 17H06047

Title: Allosteric modulation of adenosine A_{2A} receptors in mice induces slow-wave-sleep without cardiovascular effects

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Abstract: Insomnia is one of the most common sleep problems with an estimated prevalence of 10-15% in the general population and 30-60% in the older population. The adenosine A_{2A} receptor ($A_{2A}R$) agonist CGS21680 induces sleep when infused into the brain of rodents.

However, it is commonly believed that administration of an $A_{2A}R$ agonist has limited clinical potential for treating sleep disorders because of its cardiovascular side effects, including hypotension and tachycardia (de Lera Ruiz, M., *et al.*, J Med Chem, 57:3623). Moreover, all currently existing $A_{2A}R$ agonists are not suitable for treating the central nervous system due to the lack of brain permeability, as it is widely accepted that the basic adenosine scaffold must be maintained in an $A_{2A}R$ agonist. Selective physiologic $A_{2A}R$ responses may, however, be evoked by a positive allosteric modulator, because its action, in contrast to an orthosteric ligand, is limited to when and where the endogenous ligands are released. Allosteric modulation may be an alternative strategy for the treatment of insomnia, because the elevation of extracellular adenosine levels in the brain is positively associated with sleep. We established $A_{2A}R$-expressing Chinese hamster ovary cells to measure cAMP produced upon $A_{2A}R$ activation by using a fluorescence resonance energy transfer immunoassay. Subsequently, we screened several thousand small-molecule compounds for allosteric effects at $A_{2A}R$ in the cell-culture bioassay. We identified a positive allosteric modulator for $A_{2A}R$, termed YNT-378. When we examined the sleep-inducing activity of YNT-378 by monitoring the electroencephalogram, we found that the intraperitoneal (IP) administration of YNT-378 dose dependently (30-75 mg/kg) increased the total amount of slow wave sleep (SWS). The SWS-inducing effect of YNT-378 was suppressed by $A_{2A}R$ antagonist ZM241385 (15 mg/kg, IP) and abolished in $A_{2A}R$ knockout mice. In contrast to $A_{2A}R$ agonist CGS21680, blood pressure measured by using an electrosphygmomanometer and heart rhythm monitored by using electrocardiography were not affected after IP administration of YNT-378. Small molecules like the $A_{2A}R$ allosteric modulator YNT-378 may help people with sleep problems to fall asleep.

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Poster

072. Sleep: Molecular Mechanisms

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Title: Glutamate and adenosine, basal forebrain and cortex: Cross-talk during prolonged wakefulness

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Abstract: Recently we described a biochemical cascade which is critical in promoting recovery sleep (RS) after sleep deprivation (SD). It is initially triggered in the basal forebrain (BF) and later in the prefrontal cortex (PFC). This cascade includes production of inducible nitric oxide synthase (iNOS)-dependent NO followed by an increase in adenosine (AD). We hypothesized that iNOS induction is triggered by an increase in extracellular glutamate (Glu), and that the increase in AD prevents further rise in Glu via its inhibitory action on AD A1 receptor (A1R). To test this hypothesis, during 8h of SD, we first examined the time course of Glu and AD in BF/PFC. Further, to investigate the role of BF Glu receptors (GluRs) in this cascade, we measured the changes in BF/PFC AD and NREMs/delta after: a) stimulating BF GluRs by NMDA or AMPA without SD; b) blocking BF GluRs during SD by NMDAR or AMPAR selective antagonists. Finally, we measured Glu in the BF/PFC after blocking A1R. Furthermore, to determine the cellular target of glutamate effects, we examined the effects BF AMPA infusion on BF/PFC AD and NREMs/delta after BF cholinergic (ChBF) lesions using 192 IgG-saporin. Male rats were implanted with EEG/EMG recording electrodes and microdialysis guide cannulae targeting the BF and PFC. Microdialysis samples were collected during 8h SD and/or drug infusion. AD and Glu were measured using high performance liquid chromatography (HPLC) and ultra HPLC. To block NMDAR/AMPAR/A1R we used dizoclipine (MK-801)/6,7-dinitroquinoxaline-2,3-dione (DNQX)/8 cyclopentyltheophylline (CPT), respectively. 1) In the BF, Glu dramatically increased at the beginning of SD, followed by increase in AD at 2nd h of SD. When AD maximized at 4thh of SD, Glu concurrently decreased to baseline. High AD levels were maintained till the end of SD. In the PFC, Glu significantly increased within 2h of SD. When AD increased at 5thh of SD, Glu returned to the baseline. 2) BF AMPA mimicked the effects of SD by increasing AD in both BF and PFC. NREMs/delta increased post AMPA-infusion. NMDA was not effective. 3) BF DNQX prevented AD increase during SD in BF/PFC and attenuated RS. MK-801 did not show any effect. 4) CPT Infusion to the BF/PFC induced dramatic increase in Glu till the end of SD. 5) Lesion of ChBF prevented BF/PFC AD increase during AMPA infusion and attenuated NREMs/delta post-infusion. A rapid increase in Glu during SD may be a trigger for the induction of iNOS-NO-AD cascade in both the BF and PFC. AD via A1R exerts a negative feedback on Glu neurotransmission, preventing its further rise and potential toxicity during long-term SD. The effect of Glu on SD-induced changes is primarily mediated via AMPAR, located on ChBF cells.

Disclosures: A.A. Larin: None. **S.A. Karpova:** None. **R.W. McCarley:** None. **R. Basheer:** None. **A.V. Kalinchuk:** None.

Poster

072. Sleep: Molecular Mechanisms

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Support: Washington State University Commercialization Gap Fund,

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Title: A novel method for sleep disruption in rodents using home-cage based, automated sleep fragmentation

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Abstract: Sleep deprivation is associated with neurological and physiological changes that lead to cognitive and behavioral impairments. Current rodent sleep deprivation research suffers from systemic introduction of stress to the laboratory animal, interference in EEG recording signals, and inadequate induction of sleep fragmentation. We developed a new standard in rodent sleep restriction research through our Rodent Home-Cage Sleep Fragmentation Platform. Our apparatus uses periodic physical disruption to prevent a rodent from sleeping for a period of time. Unique to this design, a rodent's unmodified home chamber is placed on our platform during the sleep deprivation experiment, thereby reducing confounding variables such as environmental novelty. In combination with vibration, our platform disrupts sleep by requiring the rodent to avoid a linearly-cycling agitator that is placed within the housing chamber. We found that this method for sleep fragmentation was capable of restricting sleep in rats implanted with EEG electrodes for 6h and 12h periods, compared to gentle handling. Additionally, we found an increase in the oxidation marker, 8-OXO-dG, in prelimbic medial prefrontal cortical neurons co-labeled with parvalbumin or *Wisteria floribunda* agglutinin following 6hr sleep fragmentation using our platform. These results indicate that sleep disruption using our device leads to long lasting changes in neural signaling, similar to effects resulting from gentle handling-induced sleep deprivation. Environmental novelty and novelty-induced cellular or molecular changes in the brain can confound results and mask experimental manipulations. Reduced environmental disruption to the rodent makes this device an important improvement for

sleep research. Our platform is a significant distinction from current methods and is beneficial for rodent behavioral studies.

Disclosures: **J.H. Harkness:** 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.; WSU Commercialization Gap Fund. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cofounder, Rewire Neuroscience. LLC. **R.P. Todd:** 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.; WSU Commercialization Gap Fund. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cofounder, Rewire Neuroscience. LLC. **W. Clegern:** None. **J.P. Wisor:** None. **B.A. Sorg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership interest in device.

Poster

072. Sleep: Molecular Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Support: JSPS KAKENHI Grant Number 15K18892

Title: An *In vivo* assay method for natural sleep-promoting substances

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Abstract: The importance of sleep has recently been emphasized throughout the world as there are many people who have sleep problems in the modern world. For example, a meta-analysis has revealed that approximately 30 % of the general population present with insomnia symptoms.
We have contributed to the search for substances that promote natural sleep from natural resources, in research using electroencephalographic analyses of mice. However, electroencephalographic analysis is not suitable as a screening assay method because it requires time-consuming, labor-intensive procedures prior to measurement and in analyzing the results. Then we developed a new and easy in vivo assay method to screen sleep-promoting substances

by measuring body temperature and skin blood flow.
Changes in body temperature are generally associated with concomitant changes in sleep propensity. As sleep begins, body temperature drops; it continues to decrease during sleep, then gradually rises with awakening. Body temperature decreases because of the release of heat from peripheral sites and blood flow is a key factor in effective heat release. Then we paid attention to the variation of body temperature and skin blood flow during sleep inducement. In this study, we examined variation of them in sleep inducement, using a thermography and 2D-image laser-Doppler blood flowmeter. The test subjects were mice administered with sleeping drugs or sleep-promoting substances.
Results showed that all sleeping drugs and sleep-promoting substances decreased body temperature of mice with the same timing and duration for sleep. Additionally, this decrease was specific to sleeping drugs or sleep-promoting substances. These results showed that the monitoring of the thermal release from peripheral sites during the sleep inducement might be useful when searching for substances that can induce sleep. On the other hand, results of blood flow were different. Some agents (classical benzodiazepine drugs or diphenhydramine) decreased skin blood flow but others (ramelteon, yokukansan, glycine, L-ornithine) didn't. There are many reports about side effects and the potential risk of tolerance and dependence on the hypnotic drugs that decreased skin blood flow. On the other hand, no serious side effects have been reported in sleeping substances that didn't decrease skin blood flow. Therefore, the results of this study suggest that it is possible to screen natural sleep-promoting substances by measurement of skin temperature and skin blood flow during sleep inducement.

Disclosures: **Y. Ogawa:** None. **A. Minamizawa:** None. **S. Tada:** None. **T. Konishi:** None.

Poster

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Topic: F.08. Biological Rhythms and Sleep

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P50 MH103222

Title: Acute kynurenine challenge disrupts sleep-wake architecture and impairs contextual memory in adult rats

Authors: *A. POCIVAVSEK[1], A. M. BARATTA[1], J. A. MONG[2], S. S. VIECHWEG[2]
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Abstract: Tryptophan metabolism via the kynurenine pathway may represent a key molecular link between sleep loss and cognitive dysfunction. Modest increases in the kynurenine pathway metabolite kynurenic acid (KYNA), which acts as an antagonist at N-methyl-D-aspartate (NMDA) and α7 nicotinic acetylcholine (α7nACh) receptors in the brain, result in cognitive impairments. As glutamatergic and cholinergic neurotransmission are also critically involved in modulation of sleep, our current experiments tested the hypothesis that elevated KYNA adversely impacts sleep quality. Adult male Wistar rats were treated with vehicle (saline) and kynurenine (100 mg/kg), the direct bioprecursor of KYNA, intraperitoneally at zeitgeber time (ZT) 0 to rapidly increase brain KYNA. Levels of KYNA in the brainstem, cortex, and hippocampus were determined at ZT 0, ZT 2, and ZT 4 and our data indicate a transient increase in brain KYNA, peaking at ZT 2 (N = 5 per group). In separate animals, sleep-wake behavior was monitored with implantable telemetric devices to acquire polysomnographic recordings that combine electroencephalogram (EEG) and electromyogram (EMG) (N = 7 per group). Analyses of vigilance state-related parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM), as well as spectra power analysis during NREM and REM were assessed for 24 h after vehicle or kynurenine treatment. When KYNA levels were significantly elevated in the brain, REM duration was reduced by -53% and wake duration was increased to +150% compared to vehicle treatment. REM and wake architecture, assessed as number of vigilance state bouts and average duration of each bout, and theta power during REM were significantly impacted. Separate animals were tested in the passive avoidance paradigm, testing contextual memory. Animals were treated with vehicle or kynurenine at ZT 0 and trained in the task at ZT 2 (N = 9 - 10 per group). The next day, during the retention trial, animals treated with kynurenine were significantly impaired in the hippocampal-dependent contextual memory task. Our findings place new attention on KYNA as both a modulator of cognition and a key molecular mechanism that regulates sleep. Our ongoing studies are designed to investigate the impact of reduced KYNA synthesis on sleep and hippocampal memory. Together, these and complementary experiments may have significant translational value to treating cognitive impairments and sleep disturbances in health and disease.

Disclosures: A. Pocivavsek: None. **A.M. Baratta:** None. **J.A. Mong:** None. **S.S. Viechweg:** None.

Poster

072. Sleep: Molecular Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Title: Microbiota-derived biosignatures for acute sleep deprivation

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Abstract: It has now become increasingly clear that microbiota communicate with the central nervous system (CNS) through the gut-brain axis. In addition to metabolic diseases, neuropsychiatric disorders including major depression have been shown to be associated with the composition of the gut microbiota, which can simulate stress-related neuroendocrine responses. Impaired sleep is a frequently found comorbidity with mental illnesses, while chronic sleep loss results in depression. On the other hand, sleep deprivation exerts antidepressant effects when applied acutely. Therefore, it is of interest to identify microbiota-derived biosignatures that are characteristic for sleep deprivation. In the present study we have conducted metabolite profiling by tandem mass spectrometry of fecal pellet extracts from sleep-deprived and control mice. We assessed microbiota secreted molecules in feces from four mouse groups; control wildtype (wt), sleep-deprived wt, control CNS-specific corticotropin-releasing hormone (CRH)-overexpressing (COE), sleep-deprived CRH-COE mice (n=8 per group, 3 month old male). The mice were individually housed in a home cage, and control feces excreted within the last 2 hours were collected at Zeitgeber time (ZT) 6. Two days later, the mice were subjected to 6 hours sleep deprivation from the onset of the light period by gentle handling, and fecal pellets were collected again at the end of sleep deprivation (ZT 6). Pooled fecal pellets were immediately frozen at -80^{o}C until further processing. Fifty percent methanol fecal pellet extracts containing hydrophilic metabolites were analyzed by time-of-flight tandem mass spectrometry and resulted in the detection of more than 4,000 molecular features. PCoA cluster analysis revealed a clear separation of fecal pellet metabolite profiles between sleep-deprived and control mice that was independent of the genotype. Thus, increased levels of stress hormone in the brain, i.e., CRH, did not interfere with gut microbiome composition. Although molecular features significantly contributing to the sleep deprivation metabolite profile remain to be identified, our preliminary results are a first step for the establishment of a biosignature for the acute sleep deprivation induced phenotype. Future studies will evaluate whether sleep deprivation specific biosignatures can also be detected in patients.

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Poster

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Title: Neural correlates of the homeostatic sleep response in mouse basal forebrain

Authors: H. BOUAOUDA[1], C. SHUKLA[1], J. T. MCKENNA[1], J. MCNALLY[1], S. WINSTON[1], A. V. KALINCHUK[1], S. THANKACHAN[1], R. E. STRECKER[1], K. DEISSEROTH[2], R. W. MCCARLEY[1], R. E. BROWN[1], *R. BASHEER[1]
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Abstract: The basal forebrain (BF) plays a key role in the homeostatic sleep response (HSR) that follows prolonged wakefulness. BF Cholinergic (Ch) neurons are thought to play a privileged role in this response, since selective lesions of these neurons abolish the HSR. However, a direct comparison of the roles of Ch and non-Ch BF neurons in the HSR has not been performed. Selective optogenetic stimulation of BF parvalbumin (PV)/GABAergic and vesicular glutamate transporter 2 (vGluT2) neurons causes arousal responses, however little is known about the role of these neurons in the HSR. Furthermore, it is unclear whether the HSR requires local interactions of Ch neurons with non-cholinergic neurons. To examine the role of three wake-promoting neuronal subtypes within BF in the HSR, ChAT-cre, vesicular glutamate transporter 2 (vGluT2)-cre and PV-Cre transgenic mice were transduced with AAV-ChR2-EYFP in BF and outfitted with EEG/EMG electrodes. We examined the effect of 4h (ZT2-ZT6) laser (473nm) illuminations (5s/min, 10ms puls e, 10 Hz for Ch and vGluT2, 40Hz for PV) on enhanced NREM sleep and NREM delta activity (0.5-4.5Hz), the markers of the HSR, during the 2h (ZT 7-8) post-stimulation period and compared it with a time-matched sham-stimulation (BL, TTL pulse without laser) day. To examine whether local Ch actions within BF are important for the HSR, in ChAT-Cre mice we also recorded the sleep response when Ch antagonists were locally applied to the BF by reverse microdialysis during optogenetic stimulation of BF-Ch neurons (optodialysis). Optogenetic stimulation of Ch (N=3) neurons induced HSR, as assessed by an increase in percent time spent in NREM sleep (BL 58 ±5% *vs* post-stim 65±2%) and increased NREM delta activity by 22±7 % ($p<0.05$) during the 2 h post-stimulation period compared to BL. In contrast, optogenetic stimulation of GABA-PV neurons did not cause HSR (time spent in NREM sleep, BL 50±4, post-stim 38±4, N=6). Preliminary observations from optogenetic stimulation of vGluT2 neurons in 1 mouse, showed a tendency toward increased HSR. In the optodialysis experiment, Ch stimulation alone increased post-stim NREM sleep by 18±1% (N=3). While reverse microdialysis of a cocktail of Ch antagonists blocked the arousal effects of Ch neurons during stimulation, the post-stim NREM sleep was increased (+41±22%)

in these mice. Our results suggest BF-Ch, but not BF-PV neurons are involved in mediating HSR. vGluT2 neurons may increase HSR by exciting BF Ch neurons. Furthermore, preliminary observations from our optodialysis study suggest that local effects of BF-Ch neurons on non-Ch neurons are not required for the HSR.

Disclosures: **H. Bouaouda:** None. **C. Shukla:** None. **J.T. McKenna:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Merck MISP. **J. McNally:** None. **S. Winston:** None. **A.V. Kalinchuk:** None. **S. Thankachan:** None. **R.E. Strecker:** None. **K. Deisseroth:** None. **R.W. McCarley:** None. **R.E. Brown:** None. **R. Basheer:** None.

Poster

072. Sleep: Molecular Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant HL007713

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Title: Normal sleep requires the astrocyte brain-type fatty acid binding protein FABP7

Authors: *J. R. GERSTNER[1], I. J. PERRON[3], S. M. RIEDY[2], T. YOSHIKAWA[4], H. KADOTANI[5], Y. OWADA[6], H. P. A. VAN DONGEN[2], R. GALANTE[3], K. DICKINSON[7], J. C.-P. YIN[7], A. I. PACK[3], M. G. FRANK[1]
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Abstract: Sleep is found widely in the animal kingdom. Despite this, few conserved pathways that govern sleep across phyla have been described. The mammalian brain-type fatty acid binding protein (Fabp7) is expressed in astrocytes, and its mRNA oscillates in tandem with the sleep-wake cycle. However, the role of in regulating sleep remains poorly understood. We found that the missense mutation FABP7.T61M is associated with fragmented sleep in humans. This

phenotype was recapitulated in mice and fruitflies bearing similar mutations: Fabp7-deficient mice and transgenic flies that express the FABP7.T61M missense mutation in astrocytes also show fragmented sleep. These results novel evidence for a distinct molecular pathway linking lipid-signaling cascades astrocytes in sleep regulation among phylogenetically disparate species.

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Poster

072. Sleep: Molecular Mechanisms

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: F.08. Biological Rhythms and Sleep

Support: Academy of Finland Grant to T. Porkka-Heiskanen

Title: The effects of sleep deprivation on microglial moprhology and functional state

Authors: *H.-K. M. WIGREN[1], S. PIIRAINEN[2], M. TIBEYKINA[2], E. PRYAZHNIKOV[2], L. KHIROUG[2], L. TIAN[2], T. PORKKA-HEISKANEN[1]
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Abstract: Introduction: Sleep deprivation (SD) activates the innate immune response, and many of the molecular immune mediators are crucially involved in sleep regulation. However, less is known about the effects of SD on microglia, the brain resident immune cells, which participate in maintaining the cellular homeostasis in their resting state and in immune response upon activation. We investigated the effects of SD on mouse microglial morphology *in vivo* by using two-photon (2P) imaging of cortical microglia in freely moving microglia reporter mice before, during and after SD. In addition, polarization of microglial population towards activation was investigated in samples collected from different brain areas (the somatosensory cortex (sCX), the hippocampus (HC) and the basal forebrain (BF)) after SD and quantified by fluorescence associated cell sorting (FACS) based on differences in surface antigen expression. **Methods:** Acute 9h SD was performed with the gentle handling method. Before SD, male $CX_3CR1^{GFP/+}$ -mice were implanted with chronic cranial windows and metal bar holders above sCX under anesthesia. After recovery, mice were habituated for staying in the airlifted Mobile HomeCage™ (Neurotar Ltd, Finland), which allows free movement while the head is firmly fixed. In order to quantify microglial morphology, repeated, circadian time-controlled imaging sessions were performed with a FV1000MPE two-photon microscope (Olympus) and Mai Tai DeepSee titanium:sapphire femtosecond laser (SpectraPhysics) system. The data was quantified using Fiji (ImageJ) and Spyder (Python) software. For microglial polarization analysis, cell

suspensions from brain samples of wildtype mice were stained with a combination of anti-mouse flow cytometric markers (CD206-FITC, MHCII-PE, CD11b-PerCP/Cy5.5, F4/80-PE/Cy7, CD45-APC), acquired on a 2-laser, 6-color Gallios cytometer under a live gate of CD11b/c^{+} and analyzed with the Kaluza flow analysis 1.3 (Beckman Coulter). Reactive/Resting state was defined based on the relative surface antigen expression.
Results: The microglia soma size in the sCX assessed from the 2P images consistently decreased during the SD as compared to BL day. During the recovery day the soma size was slightly increased (P=0,003, N=4) indicating an activation. Accordingly, no differences in microglial polarization after 9h SD in the sCX or HC samples were found when compared to untreated controls (n=10 in both groups). However, in the BF, 9h SD increased the relative number of resting microglia (P=0.031).
Conclusions: Even relatively short periods of SD modify the microglial phenotype but the effect is not uniform across brain areas.

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Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number 17J08259

JSPS KAKENHI Grant Number JP16H02839

Title: Socially anxious tendencies affect impression of the other’s happy and disgusting gazes

Authors: *Y. TSUJI[1], S. SHIMADA[2]
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Abstract: Socially anxious tendencies have potentials to be social anxiety disorder (SAD). SAD is characterized by excessive fear to a social situation associated with being evaluated or embarrassed by others, and its neural mechanism has attracted substantial attention in the literature. It is also known that SAD has negative interpretation bias to ambiguous emotion in the other's face. Here we employed an impression judgement task on other's emotional gazes to examine the negative interpretation bias in eye gaze perception, as gaze of others is known to frequently induce social anxiety. We generated emotionally ambiguous gazes (happy, disgust, or

neutral) by employing a morphing technique (disgust 10-100% in 10% steps, happy 10-100%, and neutral). Subjects were required to judge whether the stimulus was positive or negative. Thirty-two male adult subjects (aged 21.4 ± 1.21, mean ± SD) participated in the study. The participant's level of social anxiety was examined by means of the Japanese version of the Social Phobia Inventory (SPIN-J). The SPIN-J is a 17-item questionnaire, each rated on a 5-point Likert-type scale. The total score of SPIN-J ranges from 0 to 68. The subjects were assigned to the high (HSA: n = 22) or low socially anxious tendency groups (LSA: n = 10) on the basis of clinical cut-off point at 30. To examine the differences in judgment curve shape between the HSA and LSA groups, a complexed curve of logistic and Gaussian function was fitted to the subject's response curve in the impression judgement task. A Gaussian function was introduced into the model to compensate for the observed trend peaked at around 'neutral'. We calculated point of subjective equality (PSE), where positive and negative judgment probabilities are equal (50%), from the fitted curve. The PSE of HSA group (disgust = 1.2 ± 8.5%) was significantly smaller than that of LSA group (disgust = 27 ± 10 %) (Wilcoxon's Rank Sum Test: $Z = 1.97$, $p < 0.05$). We also found a negative correlation between the score of SPIN-J and PSE (correlation coefficient $r = -0.36$, $p < 0.05$). These results suggest that social anxious tendencies have a tendency to recognize ambiguous emotional gaze as negative and have high sensibility to negative emotion in the other's gaze.

Disclosures: Y. Tsuji: None. **S. Shimada:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

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Program#/Poster#: 073.02/KK33

Topic: G.05. Anxiety Disorders

Support: Medical Research Council (MRC)/IoPPN Excellence PhD studentship

Title: An fMRI investigation of active avoidance behaviour in major depression

Authors: *T. WISE, L. MARWOOD, S. C. R. WILLIAMS, A. J. CLEARE, A. PERKINS
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Abstract: Anxiety is a common and important component of major depression, but it remains poorly understood at a biological level. It is particularly unclear what neural systems underlie pathological avoidance of perceived threats. Here we sought to answer this question using a validated task involving avoidance of mild electric shocks, combined with fMRI. We tested whether function in circuits responsible for avoidance in this task was altered in patients relative to controls.18 individuals with major depression and comorbid anxiety disorders, in addition to 17 healthy controls, performed an in-scanner task involving avoiding stimuli paired with mild

electric shocks. Activity during anticipation and avoidance of threats was explored and compared between groups. Anticipation of avoidable aversive stimuli was associated with significant activation in dorsal anterior cingulate cortex and striatum relative to avoidance of non-aversive stimuli. Active avoidance of aversive stimuli was associated with activity in dorsal anterior cingulate cortex and insula relative to anticipation of non-aversive stimuli. We did not observe any differences in activation between healthy controls and patients. These results suggest that the task engaged neural systems underpinning avoidance of aversive stimuli. However the absence of any group difference between patients and controls suggests that major depression is not associated with abnormal function in these networks. Future work should investigate the neural basis of passive avoidance in major depression.

Disclosures: T. Wise: None. **L. Marwood:** None. **S.C.R. Williams:** None. **A.J. Cleare:** None. **A. Perkins:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

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Program#/Poster#: 073.03/KK34

Topic: G.05. Anxiety Disorders

Support: University of Northern Colorado

Stress and Motivated Behavior Institute

Title: Type D personality enhances eyeblink conditioning in a partial reinforcement schedule

Authors: *T. ALLEN[1,2], R. J. SERVATIUS[2,3]
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Abstract: Recent work has focused on a learning diathesis model in which a temperamental factor may influence associative learning and in turn increase risk for the development of anxiety disorders. We have found in a series of studies that individuals self-reporting high levels of behavioral inhibition (BI) exhibit enhanced acquisition of conditioned eyeblinks. In the work reported here, the exploration of how personality can influence anxiety vulnerability through associative learning was extended to include distressed (Type D) personality. Type D personality is measured with the DS14 scale which includes two subscales: negative affectivity (NA) and social inhibition (SI). Social inhibition is similar to the previously studied BI while negative affect is similar to depression. Based on prior work, we hypothesized that SI, but not NA, would be related to enhanced eyeblink conditioning. Sixty participants completed personality inventories including the Adult Measure of Behavioral Inhibition (AMBI) and the DS14. All

participants received 60 acquisition trials with a 500 ms, 1000 Hz, tone CS and a 50 ms, 5 psi corneal air puff US in either a 100% CS-US paired protocol or a partial reinforcement protocol where half of the trials were US alone trials. Behaviorally inhibited individuals acquired conditioned eyeblinks at a faster rate than non-inhibited individuals in both training protocols which replicated our previous findings. Socially inhibited individuals exhibited enhanced eyeblink conditioning as compared to non- inhibited individuals, but there was no effect of negative affectivity on eyeblink conditioning. These findings extend the personality factors which can enhance associative learning to include social inhibition as well as behavioral inhibition. Our work continues to support the utility of eyeblink conditioning as a behavioral measure for assessing the role of personality in anxiety vulnerability.

Disclosures: T. Allen: None. **R.J. Servatius:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

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Topic: G.05. Anxiety Disorders

Support: Stress and Motivated Behavior Institute, Syracuse, NY

Title: Behaviorally inhibited organisms are less negatively affected by partial reinforcement in signaled lever press avoidance: Further support for the WKY strain as a model for anxiety disorders

Authors: *D. P. MILLER[1], *D. P. MILLER[1,2], D. R. COOK-SNYDER[1], B. L. GLAESER[1], K. L. NILLES[1], T. K. REGETZ[1], R. J. SERVATIUS[2]
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Abstract: The behaviorally inhibited *Wistar-Kyoto* (WKY) strain has been studied extensively as a model for human anxiety vulnerability. WKY rats acquire signaled lever-press avoidance more rapidly and they are resistant to extinguishing the avoidance response when compared to Sprague Dawley (SD) rats (e.g., Servatius et al, 2008). Recently it was demonstrated that learning in behaviorally inhibited humans was less affected by partial reinforcement during Pavlovian eye blink conditioning (Allen et al., 2014). In the present study we compared avoidance acquisition in female WKY versus female SD rats receiving either 100% paired tone-shock trails, or 50% paired trials with 50% tone only trials. A total of 24 female WKY rats and 24 female SD rats received 20 1 min warning signal trials per session for 9 sessions. An avoidance leverpress during the warning signal resulted in no shock delivery. Failure to make an avoidance response resulted in 500 ms pulses of footshock which were terminated upon

leverpress (and hence an escape response) or 20 shock pulses, whichever came first. One half of the rats received 100% paired tone-shock trials, and one half received 50% paired trials with 50% tone only trials. Avoidance responses were recorded. WKY rats receiving 100% paired trials showed the highest levels of acquisition. SD rats receiving 50% paired trials showed very little avoidance acquisition. WKY rats receiving 50% paired trials showed levels of acquisition similar to but slightly higher than SD rats receiving 100% paired trials. Our results suggest that female WKY rats are extremely influenced by the tone-shock contingency even when it is inconsistent. Such enhanced associative learning in vulnerable populations could be a major factor in the development of anxiety and stress disorders. To further study that relationship, we are performing ongoing immunohistochemical analysis in rat brain tissue from this study that aims to identify activated regions following avoidance training.

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Poster

073. Human Studies of Stress, PTSD, and Anxiety

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Topic: G.05. Anxiety Disorders

Support: NIH Grant R00-D-C-012803

Title: Anxiety mediates human respiratory dynamics following fearful stimuli

Authors: *T. J. NOTO[1], N. ARORA[3], M. SOLTANI[4], C. ZELANO[2]
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Abstract: Recent data from our lab indicate a role for the human amygdala in cortical control of breathing. Local field potential power, measured from depth wires inside the amygdala, is enhanced upon inhalation during natural breathing and electrical stimulation directed into the amygdala induces apnea. Additional experiments from our lab show that fear-related response times are faster when stimuli are encountered during inhalation compared to exhalation. The importance of the amygdala in fear processing along with its role in breathing combine to suggest the possibility for fear-related changes in breathing. The goal of the current study is to understand how the respiratory dynamics of anxious individuals differ from non-anxious individuals in the context of fearful stimuli presented over the course of the respiratory cycle. Twenty-four healthy participants completed the State Trait Anxiety Inventory questionnaire (STAI) and participated in an emotion-recognition task. Each trial began with the presentation of a face expressing either fear or surprise. Participants were instructed to indicate the emotion

expressed by each face. Faces were presented at random timing relative to the respiratory cycle, allowing full tiling of each participant's respiratory period. This allowed us to measure changes in several features of respiration of our participant pool in response to fearful and control stimuli.We found that when fearful faces are presented when participants are inhaling, the subsequent exhale is shallower compared to exhales after surprised faces. We also found that when fearful faces are presented when participants are exhaling, the subsequent inhale is deeper compared to exhales after surprised faces. Both of these effects were more pronounced in anxious participants compared to non-anxious participants. Furthermore, we found evidence that the instantaneous phase at which a stimulus is presented mediates the extent to which an individual's subsequent breath differs from a typical breath following the other stimulus in all individuals. To test this, we found the instantaneous phase of the respiratory trace and calculated the residual between the respiratory trace following each trial onset and a bootstrapped respiratory trace following the other condition. Then we calculated the weighted circular mean of the differences induced by faces at each phase. We found that the respiratory phase that modulates the subsequent breath the most occurs just before the participant begins to inhale. This novel observation supports the idea that respiratory phase may influence how stimuli are processed and reacted to.

Disclosures: **T.J. Noto:** None. **N. Arora:** None. **M. Soltani:** None. **C. Zelano:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

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Topic: G.05. Anxiety Disorders

Support: Swedish Research Council

Title: Enhanced resistance to extinction of cued versus spatial fear memory

Authors: *G. KASTRATI, M. HELOU, J. ROSEN, F. AHS
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Abstract: The physical location of cues predicting threat can influence fear memory formation and extinction. From animal studies, it seems clear that distinct neural circuits serve cue identification and cue location. Less is however known about differences between how cues and locations are learned to predict an aversive outcome through Pavlovian fear conditioning. We performed an experiment to compare conditioning of locations with conditioning of specific cues in two groups of participants. In both groups, we presented cues in four possible locations in an immersive virtual-reality environment. In one group, the same virtual human character was presented at each of the four locations (Spatial conditioning). In the other group, a unique virtual

character appeared at each location (Cued conditioning). During fear conditioning, a mild electric shock followed character presentations at two locations (CS+), whereas presentations in the other two locations were never followed by shock (CS-). Skin conductance responses (SCR) and shock expectancy ratings served as conditioning indices. Results showed that CS-differentiation did not differ between the two groups during fear conditioning. The cue conditioning group did however exhibit slowed extinction to the CS+ relative to the spatial conditioning group as indexed by SCR. The SCR results corresponded well with shock expectancy ratings which followed the same pattern during fear conditioning and extinction. This implies that processes subserving the inhibition of fear responses to threatening spatial information and cue information differ. There may be an enhanced resistance to extinction of fear responses associated with another human compared to fear responses associated with physical locations in the environment.

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Poster

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Support: NIMH Grant 1-ZIA-MH002860

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Title: Prediction error representation in individuals with generalized anxiety disorder during passive avoidance

Authors: *J. LESHIN[1], S. WHITE[2], M. GERACI[3], E. LEWIS[4], C. TENG[5], B. AVERBECK[3], H. MEFFERT[2], M. ERNST[3], J. BLAIR[2], C. GRILLON[3], K. BLAIR[2]
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Abstract: Existing evidence suggests that reinforcement-based decision-making is impaired in generalized anxiety disorder, although the pathophysiology underlying these impairments is largely unknown. Previous work on decision-making in generalized anxiety disorder has focused on adolescents and core functional processes underpinning decision-making remain undetermined. It is particularly unclear whether the representation of reinforcement prediction error (PE) (i.e., the difference between received and expected reinforcement) is disrupted in

generalized anxiety disorder. This study sought to address these issues in adults. Forty-six un-medicated adults with generalized anxiety disorder and 32 healthy comparison subjects matched on IQ, gender, and age performed a passive avoidance task while undergoing functional MRI. Data were analyzed using a computational modeling approach. Behavioral analyses revealed that adults with generalized anxiety disorder show impaired reinforcement-based decision-making relative to healthy control subjects, echoing previous work. BOLD analyses further revealed that during feedback, adults with generalized anxiety disorder, relative to healthy control subjects, showed reduced brain activation modulated by PE within the ventromedial prefrontal cortex, ventral striatum, and other structures implicated in decision-making. In addition, adults with generalized anxiety disorder, relative to healthy control subjects, showed a reduced correlation between punishment PEs, but not reward PEs, and activity within the left and right lentiform nucleus/putamen. In all, results demonstrate significant disruption in PE signaling in adults with generalized anxiety disorder. This disruption may lead to the decision-making deficits and excessive worry reported in generalized anxiety disorder by impeding the online updating ("reality checks") between expected values and actual received rewards and punishments.

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Poster

073. Human Studies of Stress, PTSD, and Anxiety

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Program#/Poster#: 073.08/LL3

Topic: G.07. Other Psychiatric Disorders

Title: Influence of nicotine on doxorubicin and cyclophosphamide-induced spatial cognitive impairment and anxiety-like behavior in rats

Authors: *Y. KITAMURA[1,2], M. SUGIMOTO[2], E. KANEMOTO[2], A. MACHIDA[2], Y. NAKAMURA[2], N. NAITO[2], I. MIYAZAKI[3], M. ASANUMA[3], T. SENDO[1]
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Abstract: Many patients who receive chemotherapy for cancer experience depressive- or anxiety-like symptoms or cognitive impairment. However, the underlying mechanisms responsible for such symptoms during chemotherapy are still not understood. On the other hand, nicotine, a nicotinic acetylcholine receptor (nAChR) agonist, is known to have cognitive and anxiolytic effects in both animals and humans. In the present study, we examined the effects of nicotine on cognitive impairment, anxiety-like behavior, and hippocampal cell proliferation in rats that had been treated with a combination of doxorubicin and cyclophosphamide.

[METHODS] Rats were intraperitoneally injected with doxorubicin (2 mg/kg) and cyclophosphamide (50 mg/kg) once a week for 4 weeks. Nicotine (2 mg/kg, s.c.) was administered daily. [RESULTS] Combined treatment with doxorubicin and cyclophosphamide produced cognitive impairment and anxiety-like behavior in the rats. Nicotine treatment reversed the inhibition of novel location recognition induced by the combined treatment. This effect of nicotine was blocked by methyllycaconitine, a selective α7 nAChR antagonist, and dihydro-β-erythroidine, a selective α4β2 nAChR antagonist. In addition, nicotine normalized the amount of spontaneous alternation seen during the Y-maze task, which had been reduced by the combined treatment. This effect of nicotine was inhibited by dihydro-β-erythroidine. In comparison, nicotine did not affect the anxiety-like behavior induced by the combined treatment. Furthermore, the combined treatment reduced the number of proliferating cells in the subgranular zone of the hippocampal dentate gyrus, and this was also inhibited by nicotine. Finally, treatment with a combination of doxorubicin and cyclophosphamide significantly reduced hippocampal α7 nAChR mRNA expression. [DISCUSSION and CONCLUSION] These results suggest that nicotine inhibits doxorubicin and cyclophosphamide-induced cognitive impairment via α7 nAChR and α4β2 nAChR, and also enhances hippocampal neurogenesis.

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Poster

073. Human Studies of Stress, PTSD, and Anxiety

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Program#/Poster#: 073.09/LL4

Topic: G.07. Other Psychiatric Disorders

Title: Effects of mirtazapine on doxorubicin and cyclophosphamide-induced spatial cognitive impairment and anxiety-like behavior in rats

Authors: *Y. NAKAMURA[1], Y. KITAMURA[1,3], N. NAITO[1], Y. SUMIYOSHI[1], I. MIYAZAKI[2], M. ASANUMA[2], T. SENDO[3]
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Abstract: Many patients who receive chemotherapy for cancer experience anxiety- or depressive-like symptoms or cognitive impairment. However, the underlying mechanisms responsible for such symptoms are still not understood. Previously, we found that combined treatment with doxorubicin and cyclophosphamide led to anxiety-like symptoms and spatial cognitive impairment in rats. On the other hand, mirtazapine is known to have anxiolytic and antidepressive effects in both animals and humans. Mirtazapine, a noradrenergic and specific

serotonergic antidepressant (NaSSA), is an agonist of the 5-HT_{1A} receptor and an antagonist of the 5-$HT_{2A/2C}$, 5-HT_3, α_1-adrenergic, α_2-adrenergic, histamine H_1, and muscarinic M_{1-5} receptors, but it does not act at 5-HT reuptake sites. This study was undertaken to determine the effects of mirtazapine on doxorubicin and cyclophosphamide-induced anxiety-like symptoms and spatial cognitive impairment in rats. [METHODS] Rats were intraperitoneally injected with doxorubicin (5 mg/kg) and cyclophosphamide (50 mg/kg) once a week for 2 weeks. Mirtazapine (5 mg/kg, s.c.) was administered daily. We performed the light-dark test and novel location recognition tests. [RESULTS] Doxorubicin and cyclophosphamide led to anxiety-like symptoms and spatial cognitive impairment in rats. The anxiety-like symptoms and spatial cognitive impairment were reversed by mirtazapine treatment. [DISCUSSION and CONCLUSION] These results suggest that mirtazapine can reverse anticancer drug-induced anxiety and spatial cognitive impairment. Studies are underway to clarify the subtypes of serotonin receptor involved in the mechanisms by which mirtazapine improves the anxiety-like symptoms and spatial cognitive impairment seen in rats that have been repeatedly treated with doxorubicin and cyclophosphamide.

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Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.10/LL5

Topic: H.01. Animal Cognition and Behavior

Title: Cognitive bias: It may not be all about stress

Authors: *O. SOUDER[1], S. KINNEY[2], K. R. BAILEY[3]
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Abstract: Emotional state can influence decision making, especially when available information for decision making is ambiguous. Rats exposed to chronic stress over a time period of three weeks demonstrate a pessimism-like expectation for punishment rather than reward (Papciak et al, 2013). While it is clear how chronic stress affects the outlook on decision making, it is less clear how a brief period of acute stress would influence behavior and decision making when available cues are ambiguous. This study examined the impact of acute stress on decision making in male Long-Evans rats. Rats learned to associate high value (chocolate) or low value (fruit loop) food rewards with tactile cues of either course or fine sandpaper. Training continued for a period of 5 weeks in which food rewards were buried progressively deeper in cinnamon or coriander scented sawdust in black or white foraging bowls placed on the right or left side of the goal box. These cues (scent, bowl color, and side placement were counterbalanced within each group and matched between the groups to control for bias). Results from training trials indicate

rats naturally demonstrate an optimistic judgement when the sandpaper stimulus is ambiguous. It was found that rats in cohort 1 subjected to three days of acute stress (restraint, water, and footshock) and retested on the final phase demonstrated a negative cognitive bias by making decisions consistent with an expectation of a low value reward when the stimulus was ambiguous. Additional analysis revealed that time to make a decision once rats traversed from the start box through the tunnel to the goal box and made a choice selection did not differ between ambiguous and learned cues, suggesting that the novel ambiguous cue did not affect goal directed decision making. Interestingly, there was a significant difference in the direction of the cognitive bias between rats in cohort 1 and those tested in cohort 2 after acute stress. The results are discussed in the context of other environmental factors that may have influenced this difference.

Disclosures: O. Souder: None. **S. Kinney:** None. **K.R. Bailey:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.11/LL6

Topic: B.09. Physiological Properties of Neurons

Support: seed funds from Rowan University SOM

R01 MH101178

Title: Effect of predator odor stress on locus coeruleus discharge and synaptic transmission

Authors: *O. BORODOVITSYNA[1], M. FLAMINI[1], F. BUTT[1], K. MILLAR[1], D. J. CHANDLER[1,2]
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Abstract: Stress is a physiological state characterized by altered neuroendocrine signaling, behavioral arousal, and anxiety that may predispose individuals for multiple diseases including post-traumatic stress disorder (PTSD), which occurs in up to 3% of the adult population. Gaining a thorough understanding of neural circuits involved in the stress response, and how they adapt in response to stress is an important step in the development of effective treatments for PTSD and other anxiety disorders. One of the crucial brain areas activated during stress is the noradrenergic nucleus locus coeruleus (LC). LC is the main source of norepinephrine in the brain and is densely innervated by stress-responsive structures such as the amygdala and hypothalamus. During stress, these regions release corticotropin releasing factor (CRF) onto LC which depolarizes its neurons, increasing tonic output and promoting behavioral vigilance and

anxiety. We have recently shown that CRF also dose-dependently modulates excitatory synaptic transmission to the LC. To determine how a single intense stressor could affect anxiety as well as LC excitability and synaptic transmission, adult male Sprague-Dawley rats were exposed to 2,5-dihydro-2,4,5-trimethylthiazoline (TMT), a component of fox urine that is innately stressful to rodents. Rats were then sacrificed and horizontal brain slices containing LC were generated for electrophysiological experiments. Whole-cell patch clamp recordings of LC neurons showed that spontaneous excitatory post synaptic current amplitudes were significantly lower in LC neurons in stressed animals, while frequency was unaffected, suggesting post-synaptic adaptation by LC. We also found increased numbers of cFos positive nuclei in some, but not all LC cells from stressed animals, particularly in the dorsal region of the nucleus, suggesting that TMT might engage a particular module of stress-responsive LC cells. Despite these findings, no significant effect of TMT exposure on anxiety in the elevated plus maze was found at acute time points. Future studies will investigate if electrophysiological effects persist to chronic time points and are accompanied by behavioral changes. These results suggest that TMT simultaneously increases spontaneous activation, and decreases synaptic excitation of LC cells, the latter of which could be caused by decreased numbers of AMPA receptors on the cell surface. Such a mechanism could help explain how stress simultaneously increases tonic yet decreases phasic discharge in the LC, an electrophysiological correlate of a shift to agitated vigilant behavior as is seen in PTSD patient populations.

Disclosures: O. Borodovitsyna: None. **M. Flamini:** None. **F. Butt:** None. **K. Millar:** None. **D.J. Chandler:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.12/LL7

Topic: D.03. Somatosensation: Pain

Support: MR157005C

Title: Development and characterization of a preclinical model recapitulating battlefield stress

Authors: *N. SOSANYA, T. GARZA, R. CHRISTY, B. CHEPPUDIRA
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Abstract: Background: Sound/noise, physical restraint, vigorous physical activities and extreme temperature are some of the common environmental stimuli to which Service Members are often exposed to on the battlefield. As a result, the exposure to such unique battlefield specific stressors, can affect their normal psychological and physiological functions thus causing stress disorders. Indeed battlefield soldiers develop stress-induced syndromes that include

anxiety, depression and body pain. Here we report the development of a protocol to mimic battlefield setting-induced stress disorders in a rat model because such preclinical model will be instrumental to comprehend fundamental mechanisms governing stress induced syndromes and identify molecular targets leading to potential therapeutic opportunities.
Materials and Methods: Male Sprague Dawley rats were exposed to four different types of stressors: (1) sound stimulus for 30 min; (2) restraint stimulus for 4 h; (3) cold stimulus for 4h; and (4) forced swim procedure for 20 min. The order of exposure of rats to stressors was intermittent; one type of stressor was presented per day for 4 days in a week (Monday – Thursday) over 4 weeks. The anxiety level in stressed animals was assessed by defecation rate during forced swim and cold stress tests while depressive-like behaviors were assessed by measuring immobility time in the forced swim test. Additionally, the alteration in nociceptive behaviors of stressed rats was detected by using von Frey and thermal hyperalgesia tests.
Results: Four weeks of intermittent stress protocol exposure in rats increased fecal pellet output and depressive-like behavior. Notably, stressed rats developed significant mechanical allodynia and also tend to develop increased sensitivity to thermal stimuli.
Conclusion: The present study has characterized a novel protocol to model battlefield stress in rats that will aid in the study of the underlying pathological state and also to identify mechanisms of pharmacological agents that can be clinically effective against combat-related stress disorders. Our investigation is quite timely and significant due to the potential to provide a new therapeutic avenue in stress related syndromes that negatively affect Service Members performance in the battlefield and also during post-war lifespan.

Disclosures: **N. Sosanya:** None. **T. Garza:** None. **R. Christy:** None. **B. Cheppudira:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

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Program#/Poster#: 073.13/LL8

Topic: G.06. Post-traumatic Stress Disorder

Support: Department of Defense Center for Neuroscience and 450 Regenerative Medicine 300601 8.0160855510005

US Army Medical Research and Materiel Command MEM-91-2714

US Army medical Research and Materiel Command MEM- 453 91-3097

Title: P300 amplitude and latency as neural markers for tracking changes of mental health in military service members after combat deployment

Authors: *C. WANG[1,2], P. RAPP[2], D. DARMON[1,2], A. TRONGNETRPUNYA[1,2], M. COSTANZO[1,2], D. NATHAN[1,2], M. ROY[2], D. KEYSER[2]
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Abstract: Military service members (SMs) are at high risk of developing neuropsychiatric conditions such as posttraumatic stress disorder (PTSD) and major depression upon their return from combat deployment. Symptom dynamics following reintegration into civilian life may be magnified over time such that some SMs present with delayed onset and may not reach a diagnostic threshold for months to years. Monitoring the trajectory of mental health in the aftermath of combat trauma can therefore be particularly important in enhancing diagnosis. Currently, clinicians must rely on patient self-report symptom checklists to make inferences about the affected neural system, but numerous biases can lead to under- or over-endorsement. Development of direct neural markers that can track the changes of mental health may facilitate early intervention and provide objective outcomes for therapeutic treatment. In this study, we investigated the possible utility of the P300 event-related potential (ERP) as a noninvasive neural biomarker for monitoring mental health. Military SMs within 2 months of their return from a deployment to either Iraq or Afghanistan were recruited to undergo a baseline assessment, with subsequent follow-up assessment at 6 or 12 months later. At each assessment, ERPs were recorded using a visual oddball task and a set of psychological scores including CAPS, PCL-M, PHQ-9, and SF-36 were obtained. We observed that the individuals with overall improved psychological scores (N = 17) at follow-up had increased P300 amplitude, and the individuals with overall worsened psychological scores (N = 13) at follow-up had prolonged P300 latency. Building a classifier using both amplitude and latency information yields high classification accuracy in identifying whether an individual is improving or deteriorating as measured by psychological scores. In addition, the degree of change evident on aggregate psychological scores was significantly correlated with the magnitude of change in P300 amplitude ($r = -0.72$, $p < 0.0001$) and latency ($r = 0.42$, $p = 0.020$). These findings suggest that the P300 can be utilized as a quantitative biomarker for tracking the changes of mental health over long-term. It may offer clinicians an objective tool for the assessment of the dynamics of mental health, and perhaps also for monitoring recovery during treatment.

Disclosures: **C. Wang:** A. Employment/Salary (full or part-time):; HJF. **P. Rapp:** None. **D. Darmon:** None. **A. Trongnetrpunya:** None. **M. Costanzo:** None. **D. Nathan:** None. **M. Roy:** None. **D. Keyser:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.14/LL9

Topic: G.06. Post-traumatic Stress Disorder

Support: JSPS Grant JP17K01404

Title: Stress evaluation using voice in dental identification work of dead body

Authors: *Y. OMIYA[1], S. SHINOHARA[2], M. HIGUCHI[2], M. NAKAMURA[2], S. MITSUYOSHI[2], I. YAMAMOTO[3], S. TOKUNO[2]
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Abstract: Mental health disorder has become a problem in dead body related work at disaster and in order to cope with it, a screening technology that will help to check depression and stress is being sought. In recent research, it is reported in an intense experience that threatens the body and life safety leave not only psychological effects but also forms "trauma memory" in the brain, causing a physiological change in the brain. Self-administered psychological tests have been used in the past, but these are beset by problems such as reporting bias. Our relevant research was to estimate depression and stress state using voice. The advantages of analysis using voice are non-invasive and can be easily carried out.
In this research, we focus on the stress in dental identification work of dead body and evaluate the stress using voice.
In the experiment, we recorded voice before and after the workshop with the cooperation of dentists who participated in dental identification workshop of dead body. In addition, Visual Analog Scale (VAS_F) as self-administered psychological tests was carried out to evaluate subjective fatigue level. The voices were collected when the subjects read 17 fixed phrases.
In the evaluation, we analyzed three types features based on our relevant research from recorded voices as Emotion (calmness, anger, joy, sorrow, and excitement), Vitality, and Pitch Rate. We compared the value of the average of each feature at before and after the workshop. Of them, “excitement” ($P = 0.050$) and “Pitch Rate” ($P = 0.034$) feature were observed significant differences based on the paired t-test between two values. Features tended to change in the positive direction. In the relevant study which is reporting that in the past disaster dispatch of self-defense forces carried out stress measurement by blood biomarker, the result showed a tendency to fall after becoming high. We would think the features became high state by a similar reason.
We also calculated the correlation coefficient between the difference of each feature and the difference of VAS_F score at before and after the workshop. As a result, a slight correlation ($R = 0.45$) was found between “anger” and VAS_F.
Consequently, the features may be indicating that subjects became arousal state by strong mental stimulus. In PTSD, there is also a report that care immediately after receiving a shock is the key to recovery, and it is expected to be applied to stress screening using voice. In addition, a weak correlation of the emotional components of anger included in voice and VAS_F was observed, suggesting the possibility of estimating the degree of fatigue of the subject by the emotional component of anger.

Disclosures: **Y. Omiya:** None. **S. Shinohara:** None. **M. Higuchi:** None. **M. Nakamura:** None. **S. Mitsuyoshi:** None. **I. Yamamoto:** None. **S. Tokuno:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.15/LL10

Topic: G.06. Post-traumatic Stress Disorder

Support: MEXT (17H06064)

Title: Pre-existing reduced functional connectivity between cognitive control network and salience network enhances PTSD symptoms after a disaster: Evidence from a longitudinal resting state fMRI study

Authors: *A. SEKIGUCHI[1], Y. KOTOZAKI[2], M. SUGIURA[3], S. NAKAGAWA[4], R. NOUCHI[5], H. TAKEUCHI[6], C. MIYAUCHI[7], Y. TAKI[8], R. KAWASHIMA[3]
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Abstract: Many survivors of severe disasters, even those without posttraumatic stress disorder (PTSD), need psychological support. To understand the pathogenesis of PTSD symptoms and prevent the development of PTSD, the critical issue is to distinguish neurological abnormalities as vulnerability factors from acquired signs of PTSD symptoms in the early stage of adaptation to the trauma in the normal population. The neurological underpinnings of PTSD have been well characterized, but the causal relationships with the traumatic event are still unclear, because of difficulties with prospective studies. In fact, we had obtained magnetic resonance images from a group of healthy adolescents before the Great East Japan Earthquake in multiple studies performed in our laboratory. Recently, we demonstrated the smaller right ventral anterior cingulate cortex (ACC) volume contributed to PTSD symptoms after the earthquake (Sekiguchi 2013). Here, we examined twenty six non-PTSD subjects using resting state functional MRI data before the earthquake by setting the right ventral ACC as a seed ROI. We found that the PTSD symptoms after the earthquake were negatively associated with functional connectivity between the right ventral ACC and right middle frontal gyrus (MFG) at rest. These brain regions are ones of key nodes of salience network and cognitive control network, respectively. Therefore, our results suggested that reduced connectivity between cognitive control network and salience

network enhances PTSD symptoms soon after the earthquake. These networks are involved in cognitive control of emotion by synchronizing each other. The findings provide a new evidence of functional network level vulnerability for a traumatic event, and may contribute to the development of effective methods to prevent PTSD.

Disclosures: **A. Sekiguchi:** None. **Y. Kotozaki:** None. **M. Sugiura:** None. **S. Nakagawa:** None. **R. Nouchi:** None. **H. Takeuchi:** None. **C. Miyauchi:** None. **Y. Taki:** None. **R. Kawashima:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.16/LL11

Topic: G.06. Post-traumatic Stress Disorder

Support: W81XWH-11-2-0166

Title: Estimation of neuron and glial numbers in the pulvinar nucleus of the thalamus in PTSD

Authors: *K. A. YOUNG[1], W. L. BONKALE[1], C. CHEN[1], G. MILLER[1], S. SACHSENMAIER[1], J. BROWNING[1], D. A. CRUZ[2], D. E. WILLIAMSON[2]
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Abstract: The role of subcortical circuit involvement in PTSD is a topic of current scientific interest, particularly with respect to threat detection and processing. The pulvinar nucleus of the thalamus is an important node in circuits subserving both conscious and subconscious threat detection, and provides direct input to the amygdala. Hyperactive treat detection has been implicated in PTSD, and manipulation of threat biases that develop in PTSD may represent novel treatments for PTSD. Chen et al., 2012 (PMID: 23155380) found that trauma survivors with larger pulvinar volumes were more susceptible to developing PTSD, while Rabellino et al, 2016 (PMID: 27631496) report that pulvinar - amygdala connectivity was enhanced during the conscious process of threat words in PTSD. We performed a pilot post-mortem stereological study of Nissl sections from formalin-fixed hemispheres of individuals with PTSD and never-mentally-ill controls (N=12). None of the PTSD cases died from suicide, although one PTSD case had missing pulvinar tissue due to the dissection procedure and was excluded from the analysis. Analysis of covariance (ANCOVA) with age, post-mortem interval and gender as covariates found that there was a trend ($t=2.36$, $p=0.064$) for a 15% increase in the estimated total number of neurons in the pulvinar in PTSD. The estimated number of astrocytes and oligodendrocytes were also larger in PTSD, although not significantly ($p=0.18$ and $p=0.086$, respectively), with the result that there was no evidence for alterations in cell ratios in PTSD.

Additional cases need to be studied to investigate covariates such as medication and to determine whether these findings are specific to PTSD. We speculate that since the pulvinar is a region of the brain that is heavily pruned and shaped during normal brain development, the present findings may reflect the presence of an anatomical residue related to challenging developmental precursors known to confer susceptibility to PTSD.

Disclosures: K.A. Young: None. **W.L. Bonkale:** None. **C. Chen:** None. **G. MIller:** None. **S. Sachsenmaier:** None. **J. Browning:** None. **D.A. Cruz:** None. **D.E. Williamson:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.17/LL12

Topic: G.06. Post-traumatic Stress Disorder

Title: Dissecting posttraumatic stress disorder complexity: A gene expression study

Authors: *H. L. RUSCH[1], C. G. MARTIN[2], S. YUN[3], J. ROBINSON[2], N. OSIER[2], J. M. GILL[2]
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Abstract: Diagnosis and treatment of posttraumatic stress disorder (PTSD) is challenging, due to complex pathophysiological mechanisms, diverse symptoms, and high symptom overlap with comorbid conditions. This longitudinal study of service members used a whole-genome expression screen to identify dysregulated genes in peripheral blood by comparing participants: (1) with vs. without PTSD; (2) endorsing vs. not endorsing important PTSD symptom clusters; and (3) whose baseline PTSD symptoms improved vs. remained unchanged following cognitive behavioral therapy. Data were analyzed using Partek Genomics Suite at a ± 2.0-fold change magnitude with a false discovery rate ≤ 0.05. We identified dysregulated genes, including 89 probesets (94% *upregulated*) in participants with PTSD, and 1,327 probesets (98% *upregulated*) in individuals with high intrusion symptoms. At follow-up, 20 genes were *downregulated* in the PTSD group with improved symptoms after therapy. Dysregulated genes in the compared groups were implicated in many biological functions (e.g., immune response; metabolic processes; and cellular signaling), as identified by Ingenuity Pathway Analysis. This innovative study is the first to identify gene expression changes that were predictive of PTSD diagnosis, prognosis related to fundamental PTSD symptom clusters, and therapeutic response. Our findings suggest that gene dysregulation is associated with some subsets of symptoms within classic PTSD symptom clusters (e.g. intrusive symptoms) but not others; this information may be relevant to selecting informative biomarkers useful for PTSD diagnosis, prognosis, and therapeutic monitoring. Ultimately, genomic biomarkers implicated in intrusion symptoms and symptomatic

improvement may inform the development of pathway-specific targets for personalized treatment of PTSD.

Disclosures: H.L. Rusch: None. **C.G. Martin:** None. **S. Yun:** None. **J. Robinson:** None. **N. Osier:** None. **J.M. Gill:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

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Program#/Poster#: 073.18/LL13

Topic: G.06. Post-traumatic Stress Disorder

Support: DA037914

U10AA08401

Title: Influence of family history of alcohol use disorder on cognitive performance and risk for post traumatic stress in trauma-exposed adolescents and young adults

Authors: S. SUBBIE[1], A. PANDEY[1], C. KAMARAJAN[2], C. COGA[2], B. PORJESZ[3], *J. L. MEYERS[4]
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Abstract: Family history of alcohol use disorder (AUD) has been previously associated with adult post-traumatic stress disorder (PTSD). Additionally, neurocognitive impairments have been observed among individuals with PTSD or a family history of AUD. One explanation suggests shared neurocircuitry involving a hyperactive amygdala and hypoactive prefrontal cortex, which influences response inhibition. Relatively few studies have examined the influence of family history of AUD together with trauma exposure on the risk for PTSD, incorporating neurocognitive performance, and no study to our knowledge has examined this using prospective assessments throughout adolescence and young adulthood. Using data from the Collaborative Study of the Genetics of Alcoholism (COGA) prospective cohort, we investigated whether trauma-exposed adolescents and young adults who report a family history of AUD have increased risk for PTSD and/or display neurocognitive deficits, than those without a family history of AUD. COGA's prospective cohort is comprised of offspring from AUD high-risk and comparison families who were aged 12-22 at enrollment and were interviewed every 2 years since 2004 (females=1246, males=1167). Traumatic exposures were collected using the Semi Structured Assessment for the Genetics of Alcoholism (SSAGA), which assesses 14 potentially traumatic events. We investigated the interactive effects of family history of AUD and trauma

exposure (assaultive, non-assaultive, and sexually assaultive exposures) on DSM-IV PTSD symptom counts and Go/No-Go (GNG) task performance, after controlling for age, sex, income and educational attainment. A significant interaction of family history AUD and a trauma factor score was observed (β=0.147, $p<0.05$) such that adolescents who had a family history of AUD had greater risk for PTSD when exposed to multiple types of trauma compared to those with less trauma exposure with or without a family history of AUD. In addition, preliminary data suggest differences in GNG task performance, which may depend on type of trauma and exposure to multiple types of trauma. Understanding the influence of family history of AUD on the risk for PTSD could inform early intervention and treatment strategies aimed at reducing the severity and endurance of PTSD.

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Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

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Program#/Poster#: 073.19/LL14

Topic: G.06. Post-traumatic Stress Disorder

Title: Trial-to-trial P300 latency jittering explains changes of averaged P300 amplitude over time in soldiers returning from combat: A longitudinal study

Authors: *A. TRONGNETRPUNYA[1,2], P. RAPP[1], D. DARMON[1,2], C. WANG[1,2], M. COSTANZO[3,2], D. E. NATHAN[4,5], M. J. ROY[3], D. KEYSER[1]
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Abstract: Attenuation in P300 amplitude has been characterized in a wide range of neurological and psychiatric disorders such as dementia, schizophrenia, and posttraumatic stress disorder (PTSD). However, it is unclear that whether the attenuation observed in the averaged ERP is due to the reduction of neural resources available for cognitive processing, or due to the increased instability of cognitive processing speed. In this study, we investigated this problem by estimating single-trial P300 amplitude and latency using the Woody filter and examining the relations of amplitudes and latencies from the single-trial level to the averaged ERP level. ERPs were recorded from thirty military service members returned from combat deployment at two time points separated by 6-12 months. A conventional visual oddball task was used to elicit P300. We observed that, within-subjects, the extent of changes in the grand-averaged P300 amplitude over time was significantly correlated with the amount of change in latency variance

of the single-trial P300 (r=-0.59, p=0.00087). The finding suggests that the change in variance of P300 latency on a single-trial level contributes to the change in amplitudes seen at the averaged ERP level. In other words, an increase in ERP amplitude may reflect more precise and consistent neural processing on a single-trial level, while a decrease in ERP amplitude may reflect a decrease in consistency. With growing explorations into objective electrophysiologically-derived biomarkers, single-trial analysis may therefore serve as a valuable approach to assess cognitive processing and mental health.

Disclosures: A. Trongnetrpunya: None. **P. Rapp:** None. **D. Darmon:** None. **C. Wang:** None. **M. Costanzo:** None. **D.E. Nathan:** None. **M.J. Roy:** None. **D. Keyser:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

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Program#/Poster#: 073.20/LL15

Topic: G.06. Post-traumatic Stress Disorder

Support: RC2MH089983

RC2MH089924

Title: Disrupted resting-state functional connectivity in adolescents with PTSD symptoms

Authors: *J. SHEYNIN[1,2], E. R. DUVAL[1,2], J. C. SCOTT[4,5], M. ANGSTADT[2], L. ZHANG[2,6], Y. LOKSHINA[2,7], D. MURRA[2,3], R. C. GUR[4,5], R. E. GUR[4], I. LIBERZON[1,2]
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Abstract: Resting-state functional connectivity (rsFC) magnetic resonance imaging (MRI) represents a potentially powerful method for illuminating brain network function. Moreover, it has particular relevance for posttraumatic stress disorder (PTSD), where abnormalities in rsFC have recently been demonstrated. The goal of the current study was to examine rsFC in an adolescent population with PTSD symptoms (*n*=59) relative to controls (*n*=226). Using a seed-based connectivity approach, we focused on a number of well-studied networks: default-mode network (DMN), which is associated with task-independent, internally focused thought and autobiographical memory, salience network (SN), which is responsible for detecting and orienting to salient stimuli, as well as ventral and dorsal attention networks that are involved in

alerting and orienting processes, respectively. Replicating our previous findings in veterans with PTSD, current results suggest desegregation between the two opposing DMN and SN networks in the group with PTSD symptoms relative to controls. Specifically, two selected seeds in the DMN (ventromedial prefrontal cortex and posterior cingulate cortex) showed greater connectivity with an SN region (insula) in the group with PTSD symptoms. In addition, the presence of PTSD symptoms was associated with reduced connectivity between ventromedial prefrontal cortex and hippocampus, which suggests aberrant within-DMN rsFC in PTSD. In addition to replicating our previous findings, current study highlights the disequilibrium between large-scale networks subserving salience detection versus "off task" stimulus-independent processes in PTSD symptoms development/expression.

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Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.21/LL16

Topic: G.06. Post-traumatic Stress Disorder

Support: NARSAD Distinguished Investigator

Brain Health Institute, Rutgers

Title: Symptoms of trauma, depression, anxiety, rumination and autobiographical memory are related in women with sexual violence history

Authors: *H. M. CHANG, E. M. MILLON, A. L. HARRIMAN, T. J. SHORS
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Abstract: Sexual violence is a global social and mental health concern affecting women of all ages, but most experiences occur during adolescence and young adulthood. A recent survey of United States universities indicates that more than 20% of women experience sexual violence during college (Cantor el al., 2015). The present study examined mental health and memory outcomes in college-aged women with and without a history of sexual violence in their lifetime. After structured interview with the SCID, women completed self-report questionnaires for depression (Beck Depression Inventory), anxiety (Beck Anxiety Inventory), rumination (Ruminative Responses Scale), post-traumatic cognitions (Post-traumatic Cognitions Inventory) and autobiographical memories about a stressful life event (Autobiographical Memory Questionnaire), as well as a working memory task (Symmetry Span, Engle lab). Women with a

history of sexual violence (n=40) reported significantly more depressive, anxious and post-traumatic symptoms (all $p < 0.01$), more vivid autobiographical memories about a stressful life event and ruminative thoughts ($p < 0.05$) relative to women without a history (n=90). Correlations among these measures were highly significant ($p < 0.001$). Working memory scores were not different between groups. These data suggest that sexual violence can increase the rehearsal of intense stressful life memories, which may contribute to or minimally interact with rumination, symptoms of depression, anxiety, and trauma-related thoughts within individuals.

Disclosures: **H.M. Chang:** A. Employment/Salary (full or part-time):; Rutgers University. **E.M. Millon:** None. **A.L. Harriman:** None. **T.J. Shors:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.22/LL17

Topic: G.06. Post-traumatic Stress Disorder

Support: Estate of São Paulo Research Foundation (FAPESP) – grant #2014/04810-0 to Felipe Corchs

Title: A pilot study on the effects of electroconvulsive therapy over the reconsolidation of traumatic memories

Authors: *F. CORCHS[1,2], Á. C. ARAÚJO[2,1], N. DEL REAL[2,1], A. MARUM[1], N. CARUI[1], G. MIGLIORANZA[1], E. ARATANGY[1], C. GORENSTEIN[3], F. LOTUFO NETO, MD[1]
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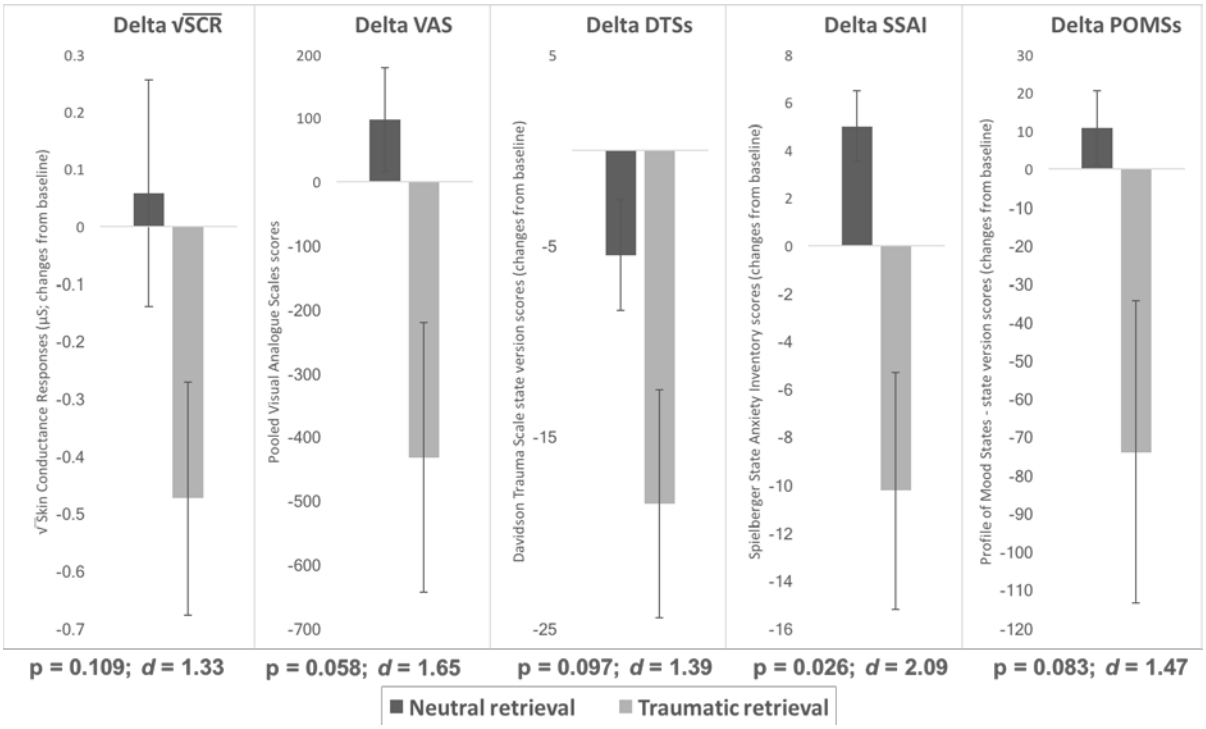
Abstract: Introduction: Subjects with Posttraumatic Stress Disorder (PTSD) seem to have extinction deficits supposed to underlie both the physiopathology and the significant rates of treatment refractoriness observed. Interventions that block the reconsolidation of the traumatic memory could compensate for this deficit. Electroconvulsive Therapy (ECT) has shown to be effective both to block the reconsolidation of aversive memories and to treat refractory PTSD. Objective: To evaluate whether ECT can interfere with the reconsolidation of traumatic memories. Methods: Eight subjects (all women, by chance) with severe, treatment-resistant PTSD (DSM-IV-TR) were randomly assigned to receive 6 sessions of ECT either after retrieving their traumatic memory (n=4) or a neutral memory (n=4). All subjects were assessed both 1 to 3 days before and 7 days after the treatment. Clinical improvement (last week symptoms) was assessed with the Davidson Trauma Scale (DTS; PTSD symptoms), the Spielberger State-Trait Anxiety Inventory (STAI, anxiety symptoms), and the Profile of Mood States (POMS, mood

symptoms). In these occasions, they were also exposed to a script-driven imagery of their traumatic event to assess Skin Conductance Responses (SCR) and subjective reactivity along the imagery, by means of Visual Analogue Scales (VAS) with symptoms of PTSD, depression, and anxiety, the state version of the STAI, and "state" adaptations of the DTS (DTSs) and POMS (POMSs). Results: Independent samples t-tests for the deltas (changes from baseline) revealed that decreases in responses to the traumatic imagery tended to be more pronounced in the pre-ECT traumatic retrieval group (X neutral retrieval) with large effect sizes (Figure 1). Clinical measurements revealed similar results: POMS (-106 ±46.3 X -8 ±42.9; p=.021; d=2.19), DTS (-48.2 ±34 X -14.5 ±23.5; p=.15; d=1.15) and STAI (-21 ±10.7 X -11 ±3.6; p=.13; d=1.25). Conclusion: retrieving the traumatic memories before ECT seems to produce strong effects. If further supported by larger samples, these results point to a promising augmentation strategy.



Disclosures: **F. Corchs:** None. **Á.C. Araújo:** None. **N. Del Real:** None. **A. Marum:** None. **N. Carui:** None. **G. Miglioranza:** None. **E. Aratangy:** None. **C. Gorenstein:** None. **F. Lotufo Neto:** None.

Poster

073. Human Studies of Stress, PTSD, and Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 073.23/LL18

Topic: H.02. Human Cognition and Behavior

Support: National Center for Advancing Translational Sciences, UL1TR000117

Henry M. Jackson Foundation for the Advancement of Military Medicine

Title: Reduced frontal cortical responses associated with cognitive changes in individuals with mtbi or ptsd during working memory

Authors: *B. WAGNER[1], W. HIGH[2], S. L. MCILWRATH[2], M. STOUT[1], L. S. BROSTER[1], R. H. LIPSKY[3,4], F. LEONESSA[5], J. B. GRIMES[5], G. S. LING[3,5], J. ECKLUND[3,5], Y. JIANG[1]
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Abstract: Combat veterans suffer from traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Both are associated with various neurological and psychiatric sequelae. However, the neural mechanisms underlying core cognitive ability, e.g. attention and working memory, are not yet well understood. Previously, we have identified Event Related Potential (ERPs) signatures associated with working memory in healthy young (Guo et al., 2008), older adults (Lawson et al. 2007), and patients with early Alzheimer's disease (Li et al., 2017). The current study investigated altered brain activity during working memory in 15 veterans vets with mTBI and/or PTSD, and 10 combat healthy controls. We hypothesize that these patterns will be different in individuals with mTBI and/or PTSD. In addition to 32-electrode scalp EEG recording as well as functional MRI brain imaging during delayed match-to-sample task, each subject completed a battery of neuropsychological tests assessing attention, processing speed, and executive function.

We revealed reduced bilateral brain responses for person with PTSD compared to controls during retrieval of memory targets using ERPs, i.e. mean amplitude of the P3 of left (-.56 vs 4.37, p=.002) and right frontal electrodes(1.15 vs 6.67, p=.003). This was also true for retrieval of nonmatch distractors at left (-0.72 vs 4.28, p=.002) and right frontal (-0.01 vs 5.07, p=.005) electrodes for PTSD compared to controls. The results from functional MRI showed similar reduced brain responses in PTSD. In the mTBIs, left frontal ERPs show reduced mean P3 amplitude compared to controls during retrieval of memory targets (4.37 vs 0.59 uV, $p < .05$), and distractors (4.28 vs -.03 mV, p =.05). Right frontal ERP differences trended towards significance in response to memory target (p=.09) but were not statistically significant in response to distractors. There is a significant correlation between left frontal P3 for retrieving target (r = -.457, p= .025), and distractor (r = -.489, p= .015), and the Trail Making Test (frontal executive functions). Interestingly, Connors performance test (attention measures) correlates with the parietal P3 (known attention-related ERPs; $p < .05$), but not with frontal ERPs.

Our findings show altered brain responses of veterans with mTBI from those of controls during working memory. Such alteration is disassociated with attention-related responses. Our findings are consistent with a recent report of reduced amplitude in individuals with PTSD or mTBI during attention and decision task at Pz sites (Gilmore et al, 2016). The mTBI brainwaves of working memory are also distinct from our reported patterns in adults with early AD.

Disclosures: **B. Wagner:** None. **W. High:** None. **S.L. McIlwrath:** None. **M. Stout:** None. **L.S. Broster:** None. **R.H. Lipsky:** None. **F. Leonessa:** None. **J.B. Grimes:** None. **G.S. Ling:** None. **J. Ecklund:** None. **Y. Jiang:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.01/LL19

Topic: G.05. Anxiety Disorders

Support: NIH R01MH108342

Title: Anxiety-like behavior is enhanced by selective knockdown of GAD67 in Neuropeptide Y interneurons in adolescent mice

Authors: *K. M. CORDER, M. A. CORTES, A. F. BARTLEY, S. A. LEAR, F. D. LUBIN, L. E. DOBRUNZ
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Abstract: GABAergic dysfunction has been implicated in a variety of neurological disorders, including anxiety disorders. Anxiety disorders are prevalent at all ages; however it is the most common disorder during adolescence. Modulation of GABA transmission through pharmacological means has been shown to regulate anxiety behaviors. GAD67 is the enzyme responsible for GABA production and a disruption in its gene has been linked to anxiety disorders. One class of GABAergic interneurons, Neuropeptide Y expressing cells, is abundantly found in brain regions associated with anxiety and fear learning, including hippocampus and amygdala. NPY has anxiolytic effects, and loss of NPY+ interneurons has been shown to enhance anxiety behaviors. Interestingly, a previous study showed that knockdown of GAD67 from NPY+ cells actually led to reduced anxiety behaviors in adult mice. However, it is unclear the role that GABA release specifically from NPY+ interneurons plays in anxiety at younger ages. To test this, we used a transgenic mouse line produced via bacterial artificial chromosome-driven miRNA silencing that reduces GAD67 in NPY+ cells (NPYGAD1-TG) and measured effects on behavior and circuit function in adolescent (1-2 month old) mice. Adolescent NPYGAD1-TG mice were found to have enhanced anxiety based on the elevated plus maze task. However, fear learning was not altered in the NPYGAD-1 TG mice. We wanted to further explore the relevance of GABA release from NPY cells in hippocampal circuit function. We found that there was an increase in a hippocampal dependent innate task, nesting behavior. However, no circuit changes were observed in the CA1 region of hippocampus. Our results show the behavioral impact of cell specific interneuron dysfunction and suggest that NPY+ cells may play different roles during development.

Disclosures: **K.M. Corder:** None. **M.A. Cortes:** None. **A.F. Bartley:** None. **S.A. Lear:** None. **F.D. Lubin:** None. **L.E. Dobrunz:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.02/LL20

Topic: G.05. Anxiety Disorders

Title: Prefrontal circuits involved in observational fear learning

Authors: *S. E. SILVERSTEIN, M. NONAKA, O. BUKALO, A. W. LIMOGES, A. HOLMES
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Abstract: Utilizing social information can provide necessary cues about safety or potential threats. While dysfunction of brain regions including the dorsomedial prefrontal cortex (dmPFC), amygdala and hippocampus are associated with risk for disorders such as psychopathy and anxiety, the neural circuitry mediating the effects of witnessed trauma remains poorly understood. To define these circuits, we first validated a mouse model of observational fear learning (OFL), in which the subject observes another mouse undergoing Pavlovian fear conditioning (30 tone+footshock pairings) and, at a later point in time, exhibits a fear reaction (freezing) to presentation of the tone. To functionally map the circuits involved in OFL, we used a retrograde tracer (Cholera Toxin B) to label inputs to the dmPFC in conjunction with co-labeling activated neurons (using c-fos as an analog of neural activation) in regions projecting to dmPFC in observing mice, demonstrators receiving a foot-shock and controls. We found a similar number of activated dmPFC-projecting neurons in brain regions associated with either fear or social learning in observers and demonstrators, as compared to controls; significant overlap was found in insula, amygdala, ventral hippocampus, claustrum, and cingulate cortex. This suggests observing a traumatic event generates a similar degree of recruitment of dmPFC-projecting brain regions as direct experience. To establish a causal role of the dmPFC in OFL, we transfected neurons in this region with a light-sensitive opsin (adenoassociated virus, ArchT3.0) to silence neuronal activity during acquisition or retrieval of OFL by shining green light directly into the dmPFC during CS-presentations. Additionally, we selectively silenced inhibitory parvalbumin-interneurons (PV) using PV-Cre transgenic mice in combination with transfusion of ArchT into dmPFC. We found that silencing the dmPFC neurons during acquisition, but not retrieval, prevented the acquisition and expression of OFL. Moreover, selectively silencing PV dmPFC interneurons at CS-presentations during OFL produced an attenuation of fear expression upon retrieval, suggesting PV interneurons in this region may be responsible for forming OFL. Ongoing studies are probing the neural inputs from the amygdala

and ventral hippocampus in a similar manner. Collectively, these data provide a novel insight into the neural circuits mediating OFL, with implications for understanding the pathophysiology of anxiety and psychological disorders resulting from witnessing trauma.

Disclosures: S.E. Silverstein: None. **M. Nonaka:** None. **O. Bukalo:** None. **A.W. Limoges:** None. **A. Holmes:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.03/LL21

Topic: G.05. Anxiety Disorders

Support: NSF Grant DGE-1110007

Title: Amygdala CRF circuits for fear and anxiety

Authors: *M. B. POMRENZE[1,2], J. TOVAR-DÍAZ[1,2], A. BLASIO[3], R. MAIYA[2,3], K. LEI[4], H. MORIKAWA[1,2], F. W. HOPF[4], R. O. MESSING[1,2,3,4]
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Abstract: Corticotropin releasing factor (CRF) has established roles in fear, anxiety, and responses to stress. The central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST) form a neuronal network (extended amygdala) that responds to aversive environments and is enriched with neuropeptides, including CRF. Extensive work implicates the CeA in the control of fear behavior and the BNST in controlling anxiety, with CRF as an essential neuropeptide to both behaviors. However, the sources of CRF and downstream regions that extended amygdala CRF neurons target to mediate fear and anxiety has only recently begun to be dissected. Here, we investigated two extended amygdala CRF populations and their contributions to fear and anxiety, using transgenic *Crh*-Cre rats and chemogenetic and optogenetic methods. We found that suppression of CeA^{CRF} neuron projections to the dorsolateral BNST prevented anxiety produced by immobilization stress, and that activation of this projection promoted anxiety. Inhibition of CeA^{CRF} neurons had minimal effects on stress-induced circulating corticosterone levels. Stimulation of CeA^{CRF} terminals with channelrhodopsin-2 in the dlBNST revealed a small number of GABA synapses on local CRF^{+} and CRF^{-} neurons. Bath application of 200 nM CRF increased the frequency of spontaneous EPSCs in CRF^{-} but not CRF^{+} neurons in the dlBNST, suggesting selective enhancement of presynaptic glutamate release onto CRF^{-} neurons. Consistent with CRF activation of the dlBNST, anxiety generated by stimulation of CeA^{CRF} terminals with hM3Dq was prevented by local blockade of CRF1 receptors. Stress-induced anxiety also depended on an intact CRF circuit

across the extended amygdala, suggesting a functional coupling between CeA^{CRF} and $BNST^{CRF}$ populations. We next assessed fear behaviors and observed that inhibition of CeA^{CRF} neurons interfered with consolidation of long-term contextual and cued fear memories. Future studies are focused on extended amygdala CRF outputs that control different aspects of fear behavior. These findings expand on early fear and anxiety models by implicating the involvement of CeA^{CRF} and $BNST^{CRF}$ neurons across multiple fear and anxiety states.

Disclosures: **M.B. Pomrenze:** None. **J. Tovar-Díaz:** None. **A. Blasio:** None. **R. Maiya:** None. **K. Lei:** None. **H. Morikawa:** None. **F.W. Hopf:** None. **R.O. Messing:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

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Topic: G.05. Anxiety Disorders

Support: NIH Grant R01MH104261

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Title: Identifying a role for glial cells in the development of affective disorders: Early-life differences in hippocampal gene expression in selectively bred rats

Authors: *P. M. MARAS[1], P. BLANDINO, Jr.[1], E. HEBDA-BAUER[1], S. WATSON[1,2], H. AKIL[1,2]
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Abstract: The development of many emotional disorders is strongly influenced by genetic factors. Using rats that have been selectively bred for their locomotor response to a novel environment, we have developed two contrasting genetic backgrounds that differ in emotional temperament: rats bred for high locomotor responses (bHRs) exhibit low spontaneous anxiety and are resilient to depression, whereas rats bred for low locomotor responses (bLRs) are highly anxious and vulnerable to depression. Importantly, we can predict adult behavioral phenotype based on lineage with almost 100% certainty and can therefore use this model to identify key developmental factors that may precede emotional dysfunction. Among the possible factors, a growing body of evidence indicates that supportive cells of the brain, including astrocytes, microglia, and oligodendrocytes, play a critical role in shaping normal brain development, and glial dysfunction may underlie many affective disorders. The exact mechanisms by which glial

cells organize emotional brain circuits and ultimately determine affective behaviors, however, remain unclear. Thus, the current set of experiments examined early postnatal expression of several glial-related genes in the bHRs/bLRs model. Hippocampal tissue samples were collected from 14-day old bHR and bLR pups, and relative mRNA levels were measured using quantitative real-time PCR. Already at this young age, robust differences in glial gene expression were evident: compared to bHRs, bLRs expressed a) higher levels of microglial markers and pro-inflammatory cytokines, b) lower levels of astrocyte-specific excitatory amino acid transporters, and c) lower levels of key myelin-related genes. Taken together, these studies reveal broad differences in an array of glial genes, such that the emotionally vulnerable bLRs appear to have elevated microglia activation and reduced astrocyte and oligodendrocyte function during a critical window of hippocampal development. Moreover, these results suggest that glial dysfunction *per se* may reflect an early factor that drives the development of affective disorders. Ongoing studies are now examining whether pharmacologically manipulating glial function during this early-life period alters the bHR/bLR phenotype, as well as the organization of the hippocampus.

Disclosures: P.M. Maras: None. **P. Blandino:** None. **E. Hebda-Bauer:** None. **S. Watson:** None. **H. Akil:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

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Program#/Poster#: 074.05/LL23

Topic: G.05. Anxiety Disorders

Support: T32DA028874

K12GM081295

DA03572

P50CA179546

Title: Circuit analysis involves the medial habenula-interpeduncular nucleus axis in anxiety-associated behavior

Authors: I. MCLAUGHLIN[1], E. E. PEREZ[1], *M. DE BIASI[2]
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Abstract: Ceasing chronic use of addictive drugs triggers an aversive withdrawal syndrome that compels relapse and deters abstinence. Many features of this syndrome are common across

multiple addictive drugs, involving both affective and somatic symptoms. Some of the circuit activity that causes withdrawal symptoms overlaps with activity associated with emotional regulation and psychiatric conditions beyond addiction, including anxiety and depression. The medial habenula (MHb) and its main projection site, the interpeduncular nucleus (IPN), have been identified as critical to the emergence of aversive states either independent of or resulting from, drug addiction. Using behavioral, chemogenetic, microdialysis, pharmacological, and viral tracing techniques *in vivo*, we show that a circuit composed of the MHb-IPN axis and serotonergic targets is involved in the manifestation of anxiety-associated behavior in mice. Specifically, we will present data describing the role of the GABAergic and glutamatergic populations of IPN neurons in regulating anxiety-related behaviors and serotonin levels in various brain areas. These data confirm a role of the MHb-IPN axis in the regulation of emotional signaling independent of drug exposure suggesting a shared neurophysiological substrate common to both addiction and mood-related psychiatric conditions.

Disclosures: I. McLaughlin: None. **E.E. Perez:** None. **M. De Biasi:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.06/LL24

Topic: G.05. Anxiety Disorders

Title: Peripheral inflammation promotes anxiety through a CRF-R1 mediated suppression of central anandamide signaling

Authors: *H. A. VECCHIARELLI, K. TAN, M. MORENA, C. M. KEENAN, M. STICHT, K. LEITL, W. HO, M. QIAO, K. A. SHARKEY, M. N. HILL
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Abstract: It is well established that there is a large degree of comorbidities between inflammatory diseases (e.g. inflammatory bowel diseases, arthritis) and stress-associated neuropsychiatric disorders (e.g. anxiety, depression). To date, however, the mechanisms underlying these comorbidities have not been fully elucidated. The endocannabinoid system regulates both anxiety and inflammation, making it a potential candidate mediating these comorbidities. To examine the hypothesis that endocannabinoids are mediators of the emotional comorbidities of peripheral inflammatory conditions, we employed an animal model of colitis to explore the potential role of endocannabinoids in these processes.
Colitis was induced by intracolonic administration of trinitrobenzene sulfonic acid (TNBS, 0.45 mL, 50 mg/mL, 50 % [vol/vol] in ethanol/water) to adult male rats, while control rats received the same volume of saline intracolonically. We previously showed, using liquid chromatography/tandem mass spectrometry, that levels of anandamide (AEA) were decreased in

the amygdala, hippocampus and medial prefrontal cortex, at seven days after the induction of colitis. These reductions in AEA content, at least within the amygdala, were related to an increase in FAAH activity, indicating that peripheral inflammation can increase central AEA hydrolysis. Concomitantly with this, we also see an increase in anxiety like-behaviour in the elevated plus maze. We now show that this increase in anxiety can be reversed with an acute intracerebroventricular administration of an inhibitor of the enzyme, fatty acid amide hydrolase (FAAH; PF04457845), which increases levels of AEA. Furthermore, we now show that at three days after the induction of colitis, when inflammation is peaking in this model, we do not see any changes in AEA levels in any brain regions examined. This could imply that AEA levels are dynamically regulated in response to colitis, with the anxiety-related reduction in AEA levels occurring following the peak of disease activity, but after a sustained period of peripheral inflammation. Furthermore, central administration of an antagonist of the corticotrophin releasing factor receptor 1 (CRF-R1; antalarmin) throughout the duration of colitis reversed the AEA reductions in the amygdala.
Together these findings add to the understanding of central mechanisms underlying anxiety-like behaviours associated with peripheral inflammation. They suggest that similar to stress-induced anxiety, inflammation-induced decreases in AEA signaling (due to CRF driving FAAH activity), are relevant for the change in anxiety-like behaviours associated with inflammation.

Disclosures: H.A. Vecchiarelli: None. **K. Tan:** None. **M. Morena:** None. **C.M. Keenan:** None. **M. Sticht:** None. **K. Leitl:** None. **W. Ho:** None. **M. Qiao:** None. **K.A. Sharkey:** None. **M.N. Hill:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

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Program#/Poster#: 074.07/LL25

Topic: G.05. Anxiety Disorders

Support: Deutsche Forschungsgemeinschaft - SFB TRR 58/A01

Title: Ultra-high field fMRI activation correlates with c-Fos cell density in the amygdala of 5-HTT knockout mice after negative stimuli

Authors: *J. F. KOLTER[1,2], M. F. HILDENBRAND[3], S. NAUROTH[2], J. BANKMANN[1], P. M. JAKOB[4], K.-P. LESCH[2], A. G. SCHMITT-BÖHRER[1]
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Abstract: The short (s) variant of the serotonin transporter-linked polymorphic region (5-HTTLPR), which results in reduced serotonin transporter (5-HTT) mRNA, 5-HTT protein and 5-HT re-uptake, is associated with several different psychiatric disorders including affective disorders and anxiety disorders. 5HTT blocking by selective serotonin reuptake inhibitors (SSRIs) is a major target for the treatment of depression. 5HTTLPR s-allele driven amygdala hyperactivity in response to negative stimuli is confirmed in humans with no psychiatric disorders. Therefore, this genotype effect in the amygdala, a brain region involved in fear processing, has to be examined in 5-HTT knockout (-/-) mice, which are the predominant model organism for the investigation of affective and anxiety disorders and have been shown to be significantly more anxious in behavioural tests compared to their wildtype (+/+) and heterozygous (+/-) littermates.
In this study, long term cerebral perfusion changes are measured by ultra-high field functional magnetic resonance imaging (fMRI) in a 17.6 Tesla Bruker Avance 750 WB system with continuous arterial spin labelling (CASL) and serve as indicator for neuronal activation. In several studies predator odours like rat soiled bedding have been used to evoke fear and are also applied in this experiment via a ventilation system. Amygdalar resting state (RS), stimulation state (SS) and post-resting **s**tate (PRS) of female and male 5HTT WT, HET and KO are measured. Subsequently, 2 hours after odor presentation, brains were dissected and immunohistochemically stained for c-Fos as marker for activation on neuronal level.
5-HTT +/+ animals show a lower RS activity, but comparable SS amygdala activity levels as 5-HTT +/- and -/- animals. The percental signal change from RS to SS is significantly higher in the 5-HTT +/+ compared to the 5-HTT +/- and -/- mice. The density of c-Fos-ir cells per μm^2 in 5-HTT +/+ is significantly higher than in 5-HTT +/- and -/- animals in all investigated amygdaloid nuclei (La, BL, Ce). The percental signal change from RS to SS correlates significantly with the density of c-Fos-ir per μm^2.
These genotype effects differ from previous studies in healthy humans and may result from different processing of visual and olfactory stimuli up to the amygdala. Hence the c-Fos-ir neurons have to be further characterized regarding their properties.

Disclosures: **J.F. Kolter:** A. Employment/Salary (full or part-time):; Deutsche Forschungsgemeinschaft (SFB TRR 58/A01). **M.F. Hildenbrand:** None. **S. Nauroth:** None. **J. Bankmann:** None. **P.M. Jakob:** None. **K. Lesch:** None. **A.G. Schmitt-Böhrer:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.08/LL26

Topic: G.05. Anxiety Disorders

Title: Resting-state fMRI reveals dopamine receptor D2 polymorphism influence on cognitive function in older healthy adults

Authors: *H. ZHENG[1], K. ONODA[1], Y. WADA[1], S. MITAKI[1], T. NABIKA[2], S. YAMAGUCHI[1]
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Abstract: Previous studies have shown that single-nucleotide polymorphisms of dopamine receptor D2 (DRD2, rs1800497) influence brain DRD2 availability which is involved in cognitive function modulation. Since neuroimaging studies suggest that resting-state network functional connectivity (FC) can serve as an imaging index for cognitive function, we speculate that DRD2 polymorphism might play a vital role in resting state brain network activity changes related to cognitive function. Thus, in the current study we aimed to investigate the effect of the DRD2 rs1800497 polymorphism on the DMN, and how it relates to cognitive function in older healthy individuals. We genotyped 99 healthy human subjects, grouping them into a T-carrier group and a C-homozygote group. Cognitive functions were evaluated by the Mini-Mental State Examination (MMSE) and Kohs' Block Design Test. We used blood oxygen level-dependent functional magnetic resonance imaging and seed-based approach to identify the DMN. The FC within the DMN was then computed across subjects. ANOVA, with factors of genotype and gender, was performed to test the group difference, and partial correlation analysis was used to explore the relationship between FC and cognitive function. We found that the FC of the left middle occipital gyrus within the DMN was significantly weaker in the C-homozygote group compared to the T-carrier group, and the FC in this region was negatively correlated with MMSE scores. Importantly, the C-homozygote group showed higher MMSE scores than the T-carrier group. Furthermore, we observed a positive correlation between the FC of the left middle occipital gyrus within DMN and Kohs' Block Design Test score in the C-homozygote group. These findings suggest that DRD2 rs1800497 polymorphism modulates FC within the DMN, and is associated with cognitive performance and visuospatial ability even before the appearance of any clinical or neuropsychological symptoms.

Disclosures: H. Zheng: None. **K. Onoda:** None. **Y. Wada:** None. **S. Mitaki:** None. **T. Nabika:** None. **S. Yamaguchi:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.09/LL27

Topic: G.05. Anxiety Disorders

Support: NARSAD Young Investigator Award #22811

Title: Dynamic changes in neuronal chromatin organization across the estrous cycle are linked to anxiety-related phenotypes

Authors: I. JARIC[1], D. ROCKS[1], J. M. GREALLY[2], M. SUZUKI[2], *M. KUNDAKOVIC[1]
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Abstract: Anxiety and depression affect~20% of the world's population and are two times more prevalent in women than in men. Sex-hormone fluctuation is likely the major risk factor for the female's increased vulnerability, although the mechanism(s) are poorly understood. Sex hormones regulate gene expression via changes in chromatin organization, which remains underexplored in the brain. Moreover, epigenetic mechanisms in the brain have been linked to anxiety-related behavior. We propose that an understanding of how fluctuating estrogen levels affect chromatin and gene expression in the brain will provide critical insights into the mechanisms underlying sex- and hormone-dependent variations in anxiety-related behaviors. To address this question, we examined female mice in two different phases of the estrous cycle: diestrus (low estrogen) and proestrus (high estrogen), and compared them to males. From 6-8 weeks of age, the estrous cycle stage was checked daily by vaginal cytological analysis and hormone levels were later confirmed by measuring estrogen levels in serum and the hippocampus. Females placed in diestrus and proestrus groups were examined with age-matched males using three anxiety tests: open-field, light-dark box, and elevated-plus maze. Across all tests, female mice in diestrus phase exhibited significantly higher indices of anxiety-like behavior compared to proestrus females and males, implying that a physiological drop in estrogen may increase risk for anxiety**.** We then assess the effects of fluctuating estrogen levels on neuronal chromatin organization in the ventral hippocampus, because neuronal activity in this area exerts a major impact on anxiety-like behavior. We performed the assay for transposase-accessible chromatin using sequencing (ATAC-seq) on FACS-purified neuronal nuclei isolated from the ventral hippocampus from each of the three groups. We detected differential chromatin accessibility in: >400 genomic regions when diestrus females were compared to proestrus females;~500 regions when diestrus females were compared to males; and 500 regions when proestrus females were compared to males. Among the regions showing estrous cycle- and sex-related chromatin (re)organization,~40% are located upstream or close to the transcription start site. These data provide novel candidate genes and pathways contributing to within- and between-sex differences in anxiety-related behavior. Unraveling the mechanisms through which sex hormones dynamically affect brain function and behavior will increase our understanding of brain sexual dimorphism and help tailor sex-specific approaches to treat depression and anxiety disorders.

Disclosures: I. Jaric: None. **D. Rocks:** None. **J.M. Greally:** None. **M. Suzuki:** None. **M. Kundakovic:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.10/LL28

Topic: G.05. Anxiety Disorders

Title: Examining the role of microbiota in emotional behavior: Antibiotic treatment exacerbates anxiety in high anxiety-prone rats

Authors: *H. MOORE[1], J. COHEN[2], J. SINGER[3], M. E. GLOVER[1], S. M. CLINTON[1]
[1]Neurosci., Virginia Tech., Blacksburg, VA; [2]Psychiatry, [3]Pathology, Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Gastrointestinal disorders are highly comorbid with affective disorders, with approximately 50% of patients with irritable bowel syndrome also exhibiting generalized anxiety disorder. An emerging view of gut microbiota highlights their roles in normal development and maintenance of a healthy gut as well as its broader effects on the immune system, central nervous system function and organismal health overall. Recent rodent studies indicate that manipulating microbiota influences brain function and emotional behavior, effects that may be mediated via changes in integrity of the blood-brain barrier. The present study builds on this work using a model of individual differences in temperament where rats were selectively bred for high versus low novelty seeking behavior. Low Novelty Responder (LR) rats exhibit high levels of anxiety- and depression-like behaviors compared to High Novelty Responders (HR). HR/LR rats display a range of neurochemical and behavioral differences. We hypothesized that HR/LR rats may exhibit microbiome differences that could contribute to their distinct neurobehavioral phenotypes. To test this, we treated adult HR/LR males with Ampicillin (0.5g/L), Neomycin (1.0g/L), and Vancomycin (0.5g/L) in their drinking water for two weeks prior to and throughout behavioral testing. 16s RNA was extracted from fecal samples to determine possible baseline HR/LR microbiome differences, as well as the impact of antibiotics on the microbiome. Somewhat surprisingly, we found that antibiotic treatment exacerbated HR/LR behavioral differences, enhancing HRs' highly exploratory phenotype while exacerbating LRs' already high levels of anxiety-like behavior. Antibiotic-treated LRs showed significantly higher levels of behavioral inhibition and greater anxiety-like behavior compared to LR controls in the Open Field Test (OFT). Antibiotic-treated HRs showed even higher levels of exploration and less anxiety-like behavior compared to control HRs in the OFT and Elevated Plus Maze. Microbiome sequencing analysis did not reveal any major differences in the composition of the baseline LR versus HR microbiome. Antibiotic treatment predictably reduced the number species present in the microbiota and it had a similar effect in HR and LR animals. Ongoing experiments are interrogating potential mechanisms whereby antibiotic treatment exaggerated HR/LR behavioral phenotypes, including examining possible effects on the blood-brain barrier. The

HR/LR lines are a powerful tool for examining the mechanisms by which microbiota contribute to neural function and animal behavior and how genetic background intersects such mechanisms.

Disclosures: H. Moore: None. **J. Cohen:** None. **J. Singer:** None. **M.E. Glover:** None. **S.M. Clinton:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.11/LL29

Topic: G.05. Anxiety Disorders

Support: MOST 103-2320-B-001-018-MY3

Title: The functional role of post-translational modification in ASIC4

Authors: *Y.-C. CHIEN[1,2], S.-H. LIN[3], C.-C. CHEN[1,4]
[1]Inst. of Biomed. Sciences, Academia Sinica, Taipei, Taiwan; [2]Program in Mol. Medicine, Natl. Yang-Ming Univ. and Academia Sinica, Taipei, Taiwan; [3]Dana-Farber Cancer Inst. and Dept. of Neurobio., Boston, MA; [4]Taiwan Mouse Clinic, Natl. Comprehensive Mouse Phenotyping and Drug Testing Center, Academia Sinica, Taipei, Taiwan

Abstract: ASIC4 is a member of acid-sensing ion channels and widely expressed the CNS. However, the physiological function of ASIC4 is still unclear. To probe the role of ASIC4, we generated an ASIC4-knockout/Cre-ERT2-knockin mouse line. Compared with wild-type littermates, ASIC4 knockouts showed higher levels of fear response (freezing) to the presence of 2,4,5-trimethylthiazoline (TMT), a component of fox urine; ASIC4 knockouts also demonstrated higher levels of anxiety-like behaviors in the open field (OF) and elevated plus maze (EPM) task. These phenotypes were opposite to the ASIC1a knockout mice, which showed lower levels of TMT-induced fear and less anxiety-like behaviors in these two mouse anxiety tasks. Based on previous results, we hypothesized that ASIC4 might modulate innate fear and anxiety state by counteracting the ASIC1a membrane protein expression. To prove this working hypothesis, we generated $ASIC4^{CreERT2/+}$::$ASIC1a^{f/f}$ conditional knockouts and screened the phenotypes in the TMT, OF and EPM tasks. Results indicated that conditional knockout of ASIC1a in ASIC4 positive neurons showed ASIC1a-like phenotypes in the innate fear and anxiety tests. We further examined whether ASIC4 knockout could affect ASIC1a protein expression in specific brain areas. Interestingly, we found ASIC1a membrane protein expression is increased in ASIC4 KO in PAG, BNST, pituitary gland, VPM/VPL, amygdala and cerebellum as compared with wildtype control. Because ASIC4 is composed of several glycosylation sites in the extracellular loop, we further generated different point mutations to see how glycosylation of ASIC4 interacts with ASIC1a and affects protein expression.

Disclosures: **Y. Chien:** None. **S. Lin:** None. **C. Chen:** None.

Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 074.12/LL30

Topic: G.05. Anxiety Disorders

Support: NIH R01 to B. Trainor

Title: Oxytocin neural circuits mediate stress induced deficits in female social behavior

Authors: *N. DUQUE-WILCKENS[1], M. Q. STEINMAN[3], M. BUSNELLI[4], S. YOKOYAMA[2], M. PHAM[2], B. CHINI[4], B. C. TRAINOR[5]
[1]Animal Behavior Grad. Group, [2]Psychology, Univ. of California, Davis, Davis, CA; [3]Committee on the Neurobio. of Addictive Disorders, The Scripps Res. Inst., San Diego, CA; [4]CNR, Milan, Italy; [5]Univ. of California -Davis, Davis, CA

Abstract: The neuropeptide oxytocin (OT) is a key regulator of social and emotional behaviors. Reports in humans that OT has prosocial and anxiolytic effects have sparked interest in the potential use of OT as a therapeutic for stress-induced psychiatric disorders. Nonetheless, it has become clear that the effects of OT are highly context dependent, and that in some cases OT could even contribute to anxiety related states. It was recently proposed that OT increases the salience of social cues, which can explain why OT can either facilitate or inhibit social behaviors. In our previous work, we found that social defeat stress increases the reactivity of OT neurons in the medioventral bed nucleus of the stria terminalis (BNST) and paraventricular nucleus in female but not male California mice. We also found that intranasal administration of OT has no effect on male social interaction, but reduces this behavior in females, mirroring the effect of social defeat stress. Here we conducted a series of experiments aimed at testing the hypothesis that stress-induced activation of OT receptors (OTR) contributes to social withdrawal in females, as well as identifying specific sites of action. First we studied the effects of systemic administration of an OTR antagonist (L-368,899, OTRA) on social behavior in control and stressed males and females. To identify potential sites of action we used immediate early gene immunohistochemistry in mice that received intranasal OT or control infusions. Based on these results, we then performed site-specific injections of OTRA in either the dorsolateral nucleus accumbens core or anteromedial BNST of stressed females. Finally, we showed that unlike some OTR antagonists (atosiban), L-368,899 does not activate G proteins but prevents OT from activating G-proteins via OTR. Our main finding is that a single dose of OTRA, either systemically or within the anteromedial BNST, rapidly reverses stress-induced social withdrawal in females. Our results support the hypothesis that stress-induced hyperactivity of OT neurons contributes to some stress-induced changes in female social behavior by activating OTR, and that

OTR antagonists may have unappreciated therapeutic potential for stress-induced psychiatric disorders.

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Poster

074. Molecules and Circuits in Preclinical Models of Anxiety

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Topic: G.05. Anxiety Disorders

Support: NIH Grant MH73136 (TZB)

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Title: Brain-wide viral genetic mapping of CRH+ neuronal inputs to the nucleus accumbens

Authors: *C. A. ITOGA[1], S. BADHON[2], C. FATERI[2], J. DELGADO[2], Y. CHEN[3], T. Z. BARAM[4], X. XU[5]
[1]Anat. & Neurobio., [2]UCI, Irvine, CA; [3]Pediatrics, [4]Univ. of California Irvine, Irvine, CA; [5]Anat. and Neurobio., Univ. California, Irvine, Irvine, CA

Abstract: Rationale: Corticotropin-Releasing Hormone (CRH) is a stress-associated neuropeptide. In addition to the regulation of the peripheral stress response by hypothalamic CRH, the peptide is expressed in limbic brain regions including amygdala and hippocampus where it plays crucial roles in emotion and cognition. CRH+ fibers are found in the nucleus accumbens (NAc), where CRH modulates reward and motivation behavior. CRH injections in the NAc amplifies incentive salience of Pavlovian cues for rewards in rodents (Pecina et al 2006) and an individual's stress history alters conditioned place preference for intra-NAc CRH injections (Lemos et al 2012). All these provide impetus to uncover the origin and circuitry of NAc CRH+ inputs.
Methods: To understand how stress-relevant brain regions and CRH+ neurons modulate NAc circuit activity and function, we used new viral genetic approaches to map CRH+ input sources to NAc in intact brains. We injected variants of a new designer rAAV2-retro (Tervo et al., 2016) that permits robust retrograde access to projection neurons with afferent inputs to the NAc;

CRH-Cre mice and rAAV2-retro DIO-CAG-tdTomato were used for specific mapping of CRH+ inputs. Both antibody immunostaining and genetic fluorescent labeling were used to confirm local CRH+ neurons in NAc and retrogradely labeled CRH+ neurons in various brain regions. Results: The primary sources of CRH+ inputs include dorsomedial and ventral subregions of the bed nucleus stria terminalis, paraventricular thalamic nucleus, basolateral and central amygdala, and the medial pre-optic area. There was only partial overlap between CRH immunoreactivity and tdTomato genetic labeling, thus indicating implications for viral-genetic manipulations of the system.
Conclusions: Together, our mapping of CRH+ inputs to NAc provide new understanding about large neural substrates underlying CRH+ modulation of reward and motivation behaviors, and offer avenues for mechanistic testing.

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Poster

075. Addiction Genetics

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: G.08. Drugs of Abuse and Addiction

Support: NARSAD Young Investigator Grant

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NIH R01DA037927

NIH P50DA039841

Title: Genome-wide mapping of ethanol sensitivity in the diversity outbred population

Authors: *E. MASIAS[1], D. GATTI[3], T. WILCOX[3], E. BUSCH[4], S. KASPAREK[1], D. KREUZMAN[1], B. MANSKY[2], S. MANSEUF[5], E. SAGALYN[5], K. SHARIF[1], D. TATERRA[1], W. TAYLOR[1], M. THOMAS[2], A. HOLMES[5], E. J. CHESLER[3], C. PARKER[1]
[1]Neurosci., [2]Middlebury Col., Middlebury, VT; [3]The Jackson Lab., Bar Harbor, ME; [4]Lab. of Behavioral and Genomic Neurosci., [5]NIAAA, Rockville, MD

Abstract: Previous mouse models have been useful in the study of alcohol use disorders (AUDs) and the identification of genetic differences that underlie initial sensitivity to the intoxicating effects of alcohol. However, their usefulness has been limited by their inability to identify

specific genes that are the basis for the physiological and behavioral traits linked to AUDs. Our study utilizes the newly developed Diversity Outbred (DO) mice, a genetically diverse and highly recombinant population. This allows for greater mapping precision, increasing the ability to identify specific gene regions as opposed to large chromosomal regions identified with previous methods. In order to identify quantitative trait loci (QTLs) associated with ethanol sensitivity, we phenotyped 778 JAX Diversity Outbred mice (DO) for three measures of ethanol sensitivity: ataxia, hypothermia, and loss of the righting response (LORR). We genotyped a subset of these mice at ~150k markers across the genome and performed high precision QTL mapping using the R program DOQTL. A paired samples t-test indicated a significant decrease in pre-ethanol performance as compared to post-ethanol performance as measured by latency to fall from the Rotarod, $t(786) = 26.6$, $p < 0.0001$, $d = .95$. A repeated-measures ANOVA indicated that following ethanol administration, subjects showed significant decreases in body temperature over time, $F(3.02, 2352.90) = 1098.30$, $p < 0.0001$, $\eta p2 = 0.59$. During LORR testing, the majority of subjects (87.7%) both lost and regained the righting reflex during the testing period, with duration of LORR ranging from 0 minutes to the cut-off time of 180 minutes ($M = 75.9$, $SD = 52.9$). Within our population, we found large variations in the three observed traits, and identified 4 significant QTLs associated with ethanol sensitivity on chromosomes 1, 9, 10, & 16 (-log10pvalue > 6.1). Our results paired with other molecular profiling and the aid of RNA-seq will allow for the identification of alleles that underlie AUDs in humans and could lead to the development of novel treatments.

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Poster

075. Addiction Genetics

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 075.02/LL33

Topic: G.08. Drugs of Abuse and Addiction

Support: 1P50 DA039841

Title: High throughput phenotyping of addiction related traits in genetically diverse mouse populations

Authors: *S. J. SUKOFF RIZZO[1], L. GAGNON[1], A. OLSEN[1], M. LEONARDO[1], R. DODD[1], T. WILCOX[1], T. ROY[1], P. DICKSON[1], M. BOGUE[1], L. REINHOLDT[1], V. M. PHILIP[1], C. H. PRATT[1], C. A. MCCLUNG[2], R. W. LOGAN[2], L. M. TARANTINO[3], J. D. JENTSCH[4], E. J. CHESLER[1]

[1]The Jackson Lab., Bar Harbor, ME; [2]Psychiatry, Univ. of Pittsburgh Med. Sch., Pittsburgh, PA; [3]Univ. North Carolina, Chapel Hill, NC; [4]Binghamton Univ., Binghamton, NY

Abstract: The Center for Systems Neurogenetics of Addiction (CSNA) brings together experts in genetics of addiction-related behavior, all focused on the identification of biological mechanisms through which predisposing behavioral trait variation influences the susceptibility for addiction. The CSNA's Behavioral Phenotyping Core (BPC) has established a streamlined behavioral testing pipeline to efficiently execute the large-scale multidimensional phenotyping efforts of the CSNA which includes evaluating neurobehavioral phenotypes of impulsivity, novelty seeking, reward seeking, and drug sensitivity. The aims of the BPC are three-fold: 1) adoption of protocols from the CSNA PIs and demonstrate through cross-laboratory assay validation the utility, robustness, reliability, and the ability to integrate the testing paradigms into a multidimensional testing battery; 2) perform behavioral characterization of diverse genetic Collaborative Cross and DO mouse populations as well as the eight founder strains (5 inbred and 3 wild-derived strains) that comprise them; and 3) provide external investigators with in-depth characterization of addiction candidate genes or novel mouse mutants using the Center's resources, expertise, and facilities to assess behavioral phenotypes relevant to both addiction-related behaviors and related co-morbidities. Data generated through the center's novelty phenotyping pipeline to date has revealed divergent behavioral phenotypes across the founder lines (A/J, 129S1/SvImJ, NOD/LtJ, NZO/H1LtJ, CAST/EiJ, PWK/PhJ, WSB/EiJ and C57BL/6J) in behavioral tests predictive of susceptibility for cocaine self-administration including phenotypes from the open field, light-dark test, exploratory holeboard, and novelty place preference which will be presented. Through collaboration with the CSNA's Integrative Genetics and Genomics Core (IGGC), the Mouse Resources and Validation Core (MRVC), and center PIs, behavioral data are being integrated with genetic information enabling the precise mapping and identification of genes and networks related to addiction. This work is supported by 1P50 DA039841 www.jax.org/csna.

Disclosures: **S.J. Sukoff Rizzo:** A. Employment/Salary (full or part-time):; The Jackson Laboratory Center for Biometric Analysis, The Jackson Laboratory Mouse Neurobehavioral Phenotyping Facility. **L. Gagnon:** None. **A. Olsen:** None. **M. Leonardo:** None. **R. Dodd:** None. **T. Wilcox:** None. **T. Roy:** None. **P. Dickson:** None. **M. Bogue:** None. **L. Reinholdt:** None. **V.M. Philip:** None. **C.H. Pratt:** None. **C.A. McClung:** None. **R.W. Logan:** None. **L.M. Tarantino:** None. **J.D. Jentsch:** None. **E.J. Chesler:** None.

Poster

075. Addiction Genetics

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 075.03/MM1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P50 DA039841

NIDA Drug Supply

Title: Detecting genetic variation in morphine LD_{50} in founder strains of the Collaborative Cross and Diversity Outbred mouse populations

Authors: *J. A. BUBIER[1], K. D. DONOHUE[2], B. F. O'HARA[3], E. J. CHESLER[1]
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Abstract: As epidemic levels of opiate abuse have spread throughout the country, overdose has become increasingly prevalent. Understanding the mechanisms and predictors of overdose and vulnerability to overdose will be critical to reducing the occurrence of these events. Given the variability in exposure patterns and life history in people with opiate addiction, research in laboratory animals can more effectively be used to characterize mechanisms of overdose liability. The laboratory mouse, with exquisite genetic capabilities can be used to identify variable mechanisms of respiratory depression and lethality associated with opioid overdose. Although there is some evidence for strain differences in sensitivity to overdose, the effects of genetic variation on morphine overdose susceptibility has been poorly characterized to date. Determining precise quantitative metrics associated with lethality is necessary to facilitate genetic dissection of the mechanisms underlying susceptibility and resistance. Using PiezoSleep monitors (Signal Solutions, LLC) to detect respiratory rhythms, we have defined an automated high-throughput technology to monitor hyperactivity and subsequent respiratory depression associated with morphine administration. The output from the PiezoSleep Mouse behavioral tracking system was analyzed using custom algorithms to estimate breath rates over small time intervals from the recorded pressure readings. This will allow determination of the duration of respiratory depression in surviving mice as well as the precise time of death in those that do not survive. We have used this system to detect statistically significant differences in the LD_{50} of morphine in 9 strains of mice including the Collaborative Cross founders and the CXBK morphine sensitive strain. With efficient, automated and precise phenotyping and evidence of substantial genetic variation in respiratory suppression, a detailed genetic analysis of the biological mechanisms of overdose risk is feasible.

Disclosures: **J.A. Bubier:** None. **K.D. Donohue:** A. Employment/Salary (full or part-time):; Signal Solutions LLC. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); subcontracts to collaborative UK laboratories that interact with our own UK laboratories. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); both founders and owners of Signal Solutions LLC, and have patents and other IP at various stages of development. **B.F. O'Hara:** A. Employment/Salary (full or part-time):; part time, Signal Solutions LLC. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); subcontracts to collaborative UK laboratories that interact with our own UK laboratories.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); we are both founders and owners of Signal Solutions LLC, and have

patents and other IP at various stages of development.. F. Consulting Fees (e.g., advisory boards); Consultant for GISMO Therapeutics and on their SAB. **E.J. Chesler:** None.

Poster

075. Addiction Genetics

Location: Halls A-C

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Program#/Poster#: 075.04/MM2

Topic: G.08. Drugs of Abuse and Addiction

Support: P50 DA039841

R01MH100241

Title: Genetic and phenotypic characterization of cocaine locomotor sensitivity using the Collaborative Cross

Authors: *S. SCHOENROCK[1], P. KUMAR[2], J. FARRINGTON[3], F. PARDO-MANUEL DE VILLENA[3], W. VALDAR[3], L. M. TARANTINO[4]
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Abstract: Substance use disorders (SUDs) are highly prevalent and result in a significant burden on the affected individual, their loved ones and society. Despite the high prevalence and personal and societal burden, very few effective treatments for SUDs currently exist. Development of effective treatments and prevention strategies has been hampered by significant gaps in our knowledge about mechanisms that increase risk for developing an SUD. It is widely accepted that both genetics and the environment contribute to SUDs and identifying the specific causal genes is critical to further our understanding of these disorders and develop effective preventive measures and treatments.
Animal models have been used to study SUDs and offer several advantages, including control of genetic background and the environment. The Collaborative Cross (CC) is an inbred mouse population that was designed to maximize phenotypic and genetic diversity and provide a platform on which to study complex systems genetics. As part of the Center for Systems Neurogenetics of Addiction (CSNA), we have identified two CC lines that are extremely divergent in their initial locomotor sensitivity to cocaine. We have characterized these lines for multiple addiction related-behaviors to advance our understanding of the relationship between initial drug sensitivity, behavioral sensitization and the rewarding and reinforcing effects of psychostimulants. We also explored the dopaminergic system, cocaine pharmacokinetics, and the hypothalamic pituitary adrenal axis as possible underlying mechanisms. Finally, we took advantage of the unique genetics of the CC to conduct a mapping study aimed at identifying candidate genes that underlie the divergent cocaine phenotypes.

We present the CC as a powerful tool for probing underlying mechanisms and discover the genes involved in the development of drug addiction and ultimately identify targets for improved treatment and prevention.

Disclosures: **S. Schoenrock:** None. **P. Kumar:** None. **J. Farrington:** None. **F. Pardo-Manuel de Villena:** None. **W. Valdar:** None. **L.M. Tarantino:** None.

Poster

075. Addiction Genetics

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Program#/Poster#: 075.05/MM3

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA028420

NIH 2016 P50 DA

Title: Research reproducibility and replicability in the Mouse Phenome Database

Authors: *M. BOGUE, E. J. CHESLER
The Jackson Lab., Bar Harbor, ME

Abstract: Replicability and the cumulative nature of knowledge are cornerstones of the scientific process. Irreproducible research in the life sciences contributes to the high cost of diagnostic and therapeutic improvements for human health. NSF, NIH and several leading journals have responded to these concerns with recommendations for practical and systematic changes to address issues associated with irreproducibility. Many of the failures associated with irreproducibility have reasonable explanations, including protocol, reagent, genetic strains, and laboratory environment differences that occur across studies when conditions are not adequately described in a reproducible manner. MPD is an online research resource providing access to primary experimental data and detailed protocols in the predominant genetic model organism, the laboratory mouse. We are developing robust methods to evaluate replicability in new and existing data relevant to neurobehavioral disorders and substance abuse from the widely used Mouse Phenome Database (MPD; phenome.jax.org). The MPD, in existence for 16 years, amasses, annotates, integrates and maintains primary quantitative phenotype data and protocols in a centralized public database. MPD has consistently provided rigorous curation of mouse experimental data to help alleviate issues associated with reproducibility and replicability. By structuring mouse phenotyping studies, annotating them to controlled vocabularies, and developing integrative tools that rely on the unique value of these data, MPD facilitates access and reuse of primary phenotype data. Integrating various sources of phenotype data in MPD provides researchers with the resources to reanalyze genetic studies with new algorithms and

genetics maps, elucidate the shared genetics for a multitude of traits, and reproduce or replicate experiments to ensure protocols and personnel are functioning properly in new environments. It should be noted that even after rigorous standardization across laboratories, non-replicable results may be observed due to the interactions among genotypes and laboratories. Using data from the MPD for a data integration effort coupled with a statistical approach that measures the variability of *GxL*, an empirically derived method to assess replicability of effects has been implemented. Together these approaches provide investigators a means to evaluate the replicability of protocols and studies in behavioral genetics research.

Disclosures: M. Bogue: None. **E.J. Chesler:** None.

Poster

075. Addiction Genetics

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Topic: G.08. Drugs of Abuse and Addiction

Support: Research funding provide by P50 DA039841 from the National Institute on Drug Addiction.

Title: Reference trait analysis facilitates the correlation of incompatible phenotypic measurements

Authors: *E. J. CHESLER, V. PHILIP, D. A. SKELLY
The Jackson Lab., Bar Harbor, ME

Abstract: Systems genetic analysis of complex traits involves the holistic analysis of genomic and disease related measures. Often a joint biological mechanism is suspected for correlated traits, but extracting such mechanisms can be physically impossible if the two traits cannot be simultaneously assayed in the same individuals, for example, in the correlation of drug naïve gene expression to drug exposure related behavior. We propose a simple and powerful strategy for the identification of genomic correlates of complex traits estimated in unrelated individuals. In this approach, based on canonical correlation methodology, one set of “reference” traits is measured across all individuals and two incompatible sets of traits are measured in disjoint subsets of these individuals. The incompatible traits are of primary interest but cannot be measured in the same individual, for example brain transcriptional profiling and behavioral traits dependent upon treatments that alter brain physiology. Canonical correlation is used to relate the reference traits and behavioral traits, and to project behavioral variation onto the transcriptional profiles, allowing one to identify behavioral trait-transcript correlations. We test this methodology using a behavioral genetics experiment in Diversity Outbred mice where we study relationships between anxiety related behaviors and hippocampal gene expression. The highest

canonical correlation (R = 0.69) between anxiety measured using two assays, the open-field test and the light-dark test, enabled extraction of transcripts correlated to both measures.

Disclosures: E.J. Chesler: None. **V. Philip:** None. **D.A. Skelly:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: 1P50 DA039841

Title: Identification and validation of novel addiction mutants using addiction predictive phenotypes

Authors: *V. M. PHILIP[1], T. WILCOX[2], T. A. ROY[2], P. E. DICKSON[2], J. A. BUBIER[2], E. J. CHESLER[2]
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Abstract: The Jackson Laboratory's Knockout Mouse Phenotype (KOMP) pipeline has been characterizing drug naïve single gene knock-outs across several behavioral and physiological phenotypes. Included in these behavioral phenotypes are phenotypes related to novelty, depression and anxiety. Several studies have shown that these baseline behaviors are correlated to and predictive off addiction relevant phenotypes. There this association can be exploited towards the identification of novel genes for substance addiction. We applied a multivariate analysis approach using these addiction predictive phenotypes, across all KOMP mutants characterized thus far, to identify "outlying" addiction mutants. These mutants are expected to behave as hyper- or hypo- active on either all or a subset of addiction predictive phenotypes, thereby making them ideal candidates for further validation on addiction relevant paradigms. Validation of these addiction mutants were performed using oral drug self-administration and drinking in the dark paradigms.

Disclosures: V.M. Philip: None. **T. Wilcox:** None. **T.A. Roy:** None. **P.E. Dickson:** None. **J.A. Bubier:** None. **E.J. Chesler:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: PHS Grant 1P50 DA039841

PHS Grant R21 DA038377

Title: SYN3, encoding synapsin III, regulates reversal learning in mice

Authors: *J. D. JENTSCH, J. LINDEN, A. S. JAMES
Binghamton Univ., Binghamton, NY

Abstract: Impairments in inhibitory self-control likely play a critical role in the development and maintenance of problematic/hazardous patterns of drug and alcohol abuse. Emerging evidence from human subjects and animal models suggests that inhibitory control capacity is a heritable phenotype that predicts inter-individual variability in the alacrity to initiate drug or alcohol use. For this reason, discovering genetic variants linked with poor inhibitory control may reveal novel insights into the genetic and genomic influences linked with vulnerability for addictive behaviors. Genome-wide linkage and association studies conducted by our lab using inbred mouse panels identified *SYN3*, encoding the synaptic phosphoprotein synapsin III, as a potential candidate gene influencing inhibitory control abilities measured using a reversal learning task. Specifically, variants contained within the *SYN3* locus that were associated with low *SYN3* expression were correlated with poorer inhibitory control. We therefore hypothesized that engineered mice that underexpress synapsin III would exhibit reversal learning deficits. We evaluated mice carrying 0, 1 or 2 null mutations in the *SYN3* gene on a reversal learning task. There were no differences between genotype groups in their ability to learn a simple visual discrimination task. As expected, all genotype groups required 2-3.25 times more trials to reach criterion in the reversal learning condition, and, when individually compared to wild-type littermate controls, the heterozygous and homozygous mutant animals exhibited more difficulty with learning the reversal. Measures of motor speed and motivation to engage in the task were not different between genotype groups. These data suggest that loss of function of the *SYN3* gene and/or underexpression of the synapsin III protein can negatively impact inhibitory control abilities in mice, thereby supporting the idea that it may represent an addiction-relevant candidate gene.

Disclosures: **J.D. Jentsch:** None. **J. Linden:** None. **A.S. James:** None.

Poster

075. Addiction Genetics

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Title: A common SNP in Chrna5 attenuates dopamine release from the nucleus accumbens in response to morphine

Authors: *J. K. BRYNILDSEN[1], E. PEREZ[2], M. DE BIASI[2], J. A. BLENDY[1]
[1]Systems Pharmacol. and Translational Therapeut., [2]Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The single nucleotide polymorphism (SNP) D398N (rs16969968) in *CHRNA5,* the gene encoding the α5 subunit of nicotinic acetylcholine receptors, has been repeatedly associated with nicotine dependence in human populations, and at least one study has identified an association of this SNP with opioid dependence severity. Expression of this SNP in presynaptic VTA neurons is shown to cause a reduction in calcium signaling, leading to alterations in transmitter signaling and altered response to drugs of abuse. To examine the signaling mechanisms underlying the proposed association between *Chrna5* SNP and opioid dependence, mice harboring two copies of the risk-associated allele (*Chrna5* A/A) at a location equivalent to human rs16969968 were generated via CRISPR/cas9 genome editing. Under drug-naïve conditions, mice bearing the SNP showed no difference in locomotor activity or anxiety-like behavior in the elevated plus (EPM) or open field (OFA) compared to wild-type (WT) mice. In vivo microdialysis was used to quantify dopamine release from the nucleus accumbens (NAc) in WT, *Chrna5* A/A, and *Chrna5* null mice. Animals were implanted with probes in the NAc and dialysate samples were collected every 20 min as follows: 4 baseline, 3 following saline injection, and 6 following morphine injection (10 mg/kg, s.c.). Dopamine concentrations measured via HPLC were normalized to baseline measurements. Two-way repeated measures ANOVA revealed a significant interaction of treatment and genotype ($p=0.01$), whereby *Chrna5* A/A and *Chrna5* null mice showed an attenuated response to acute morphine compared to WT animals. This finding suggests a reduction in α5 nAChR subunit function is associated with reduced dopaminergic sensitivity to opioids. Future studies examining the impact of this SNP on morphine reward and locomotor sensitization will determine its behavioral significance.

Disclosures: **J.K. Brynildsen:** None. **E. Perez:** None. **M. De Biasi:** None. **J.A. Blendy:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Title: Association analysis between genetic variation in the FKBP5 gene and cortisol levels in alcohol dependence

Authors: *K. MAURO, C. MUENCH, J. LEE, M. SCHWANDT, A. ROSEN, J. SORCHER, D. ROSOFF, F. LOHOFF
NIAAA-NIH, Bethesda, MD

Abstract: Previous research has shown an association between altered HPA axis regulation and alcohol use and dependence. This alteration is manifested by elevated cortisol during acute withdrawal, while early abstinence typically involves low cortisol production and a blunted cortisol response to stress. Research has shown that while alcohol use might contribute to this change in the functionality of the HPA axis, the axis' alteration may precede the development of alcohol dependence through genetic factors and trauma exposure. Both preclinical and clinical research have implied the gene *FKBP5* as an important regulator of cortisol. *FKBP5* encodes the glucocorticoid receptor (GR) binding protein FK506-binding protein 5(FKBP5), which decreases the GR affinity for cortisol, thereby altering the HPA axis' negative feedback system. Previous studies suggest that single-nucleotide polymorphisms (SNPs) in *FKBP5* increase risk for the development of post-traumatic stress disorder following childhood trauma exposure, as well as influence the severity of alcohol withdrawal. The present study aimed to examine the association between *FKBP5* variants and morning cortisol among 212 alcohol dependent (AD) participants during acute withdrawal. Genotypes for 20 *FKBP5* SNPs were extracted from data from standard genotype arrays, Illumina Human OmniExpress-12 and Human OmniExpressExome v1.2. Association analysis for the set of SNPs was conducted using linear regression in PLINK, controlling for age, gender, and ancestry informative marker scores for European and African ancestry. Results showed that rs9380524 was the only SNP significantly associated with morning cortisol in AD participants ($p<0.002$). To correct for multiple testing, p-values for individual SNPs were adjusted using the Benjamini-Hochberg False Discovery Rate ($p<0.05$). When grouping 125 of the above AD participants based on whether or not they experienced childhood trauma, there was a significant association between rs938052 risk allele A and morning cortisol in the trauma exposed group ($p<0.002$). Our results show an association between the SNP rs9380524 in *FKBP5* and morning cortisol among AD participants, and that this association may be exacerbated by childhood trauma. This SNP has previously been implicated in alcohol

withdrawal severity, so increases in cortisol production might help explain this relationship. Additional studies of this variant are needed to determine whether it is associated with other alcohol-related phenotypes.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA030389

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Title: OPRM1 and CHRNA5 genotypes interact with an adolescent substance use prevention intervention to reduce smoking during high school

Authors: *D. J. VANDENBERGH[1,2,3], G. L. SCHLOMER[6], H. H. CLEVELAND[4], A. M. GRIFFIN[4], M. E. FEINBERG[5], M. T. GREENBERG[5,4], R. L. SPOTH[7], C. REDMOND[7]
[1]Biobehavioral Hlth., [2]The Huck Inst. for the Neurosci., [3]Mol. and Cell. Integrative Biosci. Program, [4]Human Develop. and Family Studies, [5]Bennett Pierce Prevention Res. Ctr., Penn State Univ., University Park, PA; [6]Div. of Educational Psychology and Methodology, Univ. at Albany, Albany, NY; [7]Partnerships in Prevention Sci. Inst., Iowa State Univ., Ames, IA

Abstract: The mu opioid receptor gene (*OPRM1*) contributes to genetic risk for multiple addiction-related phenotypes, including smoking. The findings for adolescent smoking, however, are less consistent. We assessed the role of genotype at SNP rs1799971 (A118G) in *OPRM1* on high school smoking in a unique sample of adolescents who had participated in a prevention intervention program, which allowed for the analysis of gene X environment (specifically the intervention) effects. Smoking in the past month was assessed in grades 9–12 using a four-point scale (0 = never smoked, 1 = smoked but not in last month, 2 = one or a few times, 3 = about once a week or more) in a sample of 1,688 participants who participated in either control condition or a family based intervention in grade 6, and a school-based drug preventive intervention in grade 7, based on random assignment of the school. There was no main effect of genotype at *OPRM1* (coded as presence/absence of the G allele) or intervention, but the interaction was significant ($b = -0.22$, $p < 0.01$). In a subsequent analysis, we extended published results of the nicotinic receptor alpha5 subunit gene (*CHRNA5*) (rs16969968) by combining genotypes at the two SNPs. There was no main effect of the combined genotype

score, but the interaction with intervention was significant ($b = -0.27$, $p < 0.01$). Our results suggest that specific genotypes might interact with prevention programs to diminish drug use, but the interaction is complex and involves multiple genes. Better methods to identify these genes need to be developed.

Disclosures: D.J. Vandenbergh: None. **G.L. Schlomer:** None. **H.H. Cleveland:** None. **A.M. Griffin:** None. **M.E. Feinberg:** None. **M.T. Greenberg:** None. **R.L. Spoth:** None. **C. Redmond:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: ZIA DA000069

Title: Empirical validation of cocaine targets in the striatum identified using big data

Authors: *R. J. ELLIS, J. L. GOMEZ, L. A. RODRIGUEZ, M. MICHAELIDES
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Abstract: Biocuration of experimental data is growing exponentially. Big data approaches are crucial for utilizing biocurated data to form coherent and novel research questions. Publicly available data about the effects of cocaine on the mouse transcriptome in brain regions relevant to addiction were analyzed using several computational tools and five candidate genes were selected for independent empirical validation. Upon quantifying the expression of these candidates in the same regions referred to in the analyzed datasets, one was confirmed as differentially expressed in the nucleus accumbens shell and is unexplored, with no published mechanistic studies of its relation to cocaine or addiction. This study supports the idea that big data approaches are essential to forming novel research questions relating to and uncovering relationships between drugs and the genome.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: 589-KG-0012 (VA)

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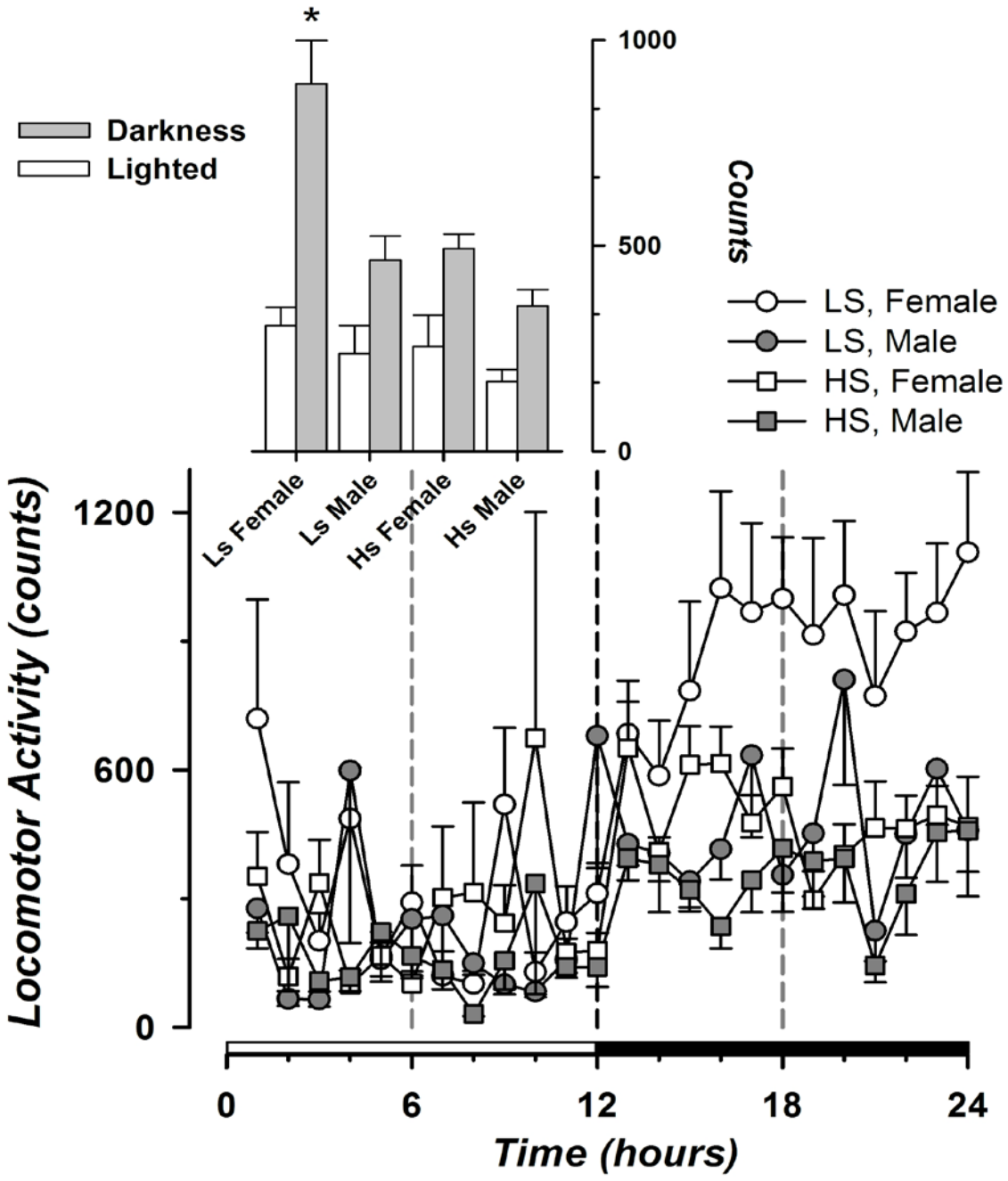
Title: Diurnal pattern of locomotor activity after selective breeding for cocaine self-administration in rats

Authors: *K. W. GRASING[1], H. XU[2]
[1]Kansas City Veterans Affairs Med. Ctr., Kansas City, MO; [2]Florida State Univ., Tallahassee, FL

Abstract: The LS and HS rat lines were selectively bred for Low and High intravenous drug Self-administration. HS rats have greater cocaine-induced activation of dopamine D1 and D2 receptors in the nucleus accumbens and ventral tegmental area, with lower extracellular dopamine and acetylcholine in the nucleus accumbens shell. The current study was designed to determine how locomotor activity varied across different times of day in LS and HS rats. METHODS: Individual LS and HS rats were isolated in sound-attenuated chambers over a period of four days while being maintained on a standard cycle of 12 lighted and 12 dark hours. Locomotor activity was detected through infrared beam breaks, collected over 24 hours on the final day of isolation. Both consecutive activations of the same infra-red detector (showing repeated activity in one place, which may reflect stereotypy), and activation of two different detectors (reflecting linear activity across the cage) were continuously recorded. RESULTS: Female LS rats exhibited greater non-repeated locomotor counts during hours of darkness, relative to either male LS rats or HS rats of either sex. Non-repeated counts during lighted (inactive) hours did not differ by strain or sex. Repeated locomotor activity did not differ across strain, sex, or time of day. CONCLUSION: Linear but not repeated locomotor activity varied in complex manner with strain and sex, with greater values observed in female rats during darkness, which corresponds to the active period of rodents. Several mutations of genes influencing biologic rhythms have been show to influence susceptibility to drug reward. These results show that similar genetic differences could also underlie altered drug reward in LS and HS rats. This model may be a productive means of investigating the biological basis for individual differences that modify susceptibility to drug reward.



Disclosures: **K.W. Grasing:** None. **H. Xu:** None.

Poster

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Title: Adolescent cocaine experience differentially augments psychomotor sensitization in adulthood and alters epigenetic profiles in the striatum and prefrontal cortex of selectively bred high- and low-responder rats

Authors: *A. PARSEGIAN[1], J. GARCIA-FUSTER[3], S. J. WATSON, Jr.[2], S. B. FLAGEL[1], H. AKIL[2]
[1]Mol. and Behavioral Neurosci. Inst., [2]Univ. of Michigan, Ann Arbor, MI; [3]IUNICS. Univ. of the Balearic Islands, Palma de Mallorca, Spain

Abstract: Parsing the impact of genetic disposition vs. environmental factors on addiction liability has proven difficult. While early initiation of drug use in adolescence reliably predicts a greater likelihood of addiction in adulthood, the molecular mechanism by which this occurs and whether genetic predisposition is involved is not known. To address this, we used a unique genetic animal model to determine the impact of adolescent cocaine experience on adult psychomotor sensitization and epigenetic profiles in several limbic brain areas. Relative to bred low-responder (bLR) rats, adult bred high-responders (bHR) are more sensitive to the psychomotor-activating effects of cocaine and reinstate drug-seeking more readily following a prolonged period of abstinence. In agreement, here we found that a sensitizing regimen of cocaine (15 mg/kg) during adolescence (PND 33-39) produced psychomotor sensitization (on PND 39) in bHRs only. However, in adulthood, bLRs with a history of cocaine exposure during adolescence shifted their phenotype, showing enhanced sensitization. We then assessed two functionally opposite epigenetic chromatin modifications on histone 3 lysine 9 (H3K9) in four

subregions of striatum and prefrontal cortex, and identified co-expression within certain cell types (e.g., D1 and D2) using a novel combination of fluorescent *in situ* hybridization, immunohistochemistry and unbiased stereology. Both the permissive acetylation (ac) and repressive tri-methylation (me3) marks have been previously shown to influence genes, downstream signaling pathways, and proteins implicated in addiction liability. Here we found that, relative to saline controls of the same phenotype, adolescent cocaine exposure reduced acH3K9 expression in the core of the nucleus accumbens of adult bHRs, but increased acH3K9 expression in the core of adult bLRs. Further, both acH3K9 and H3K9me3 expression was increased in the prelimbic subregion of the prefrontal cortex of bLRs with a history of cocaine during adolescence. Finally, expression changes were generally seen more in D1-expressing cells, as compared to D2 cell sub-types, but further classification is in progress. These results indicate that adolescent drug use can influence inborn genetic differences in addiction liability via chromatin modifications in specific brain areas of the limbic system.

Disclosures: A. Parsegian: None. **J. Garcia-Fuster:** None. **S.J. Watson:** None. **S.B. Flagel:** None. **H. Akil:** None.

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Topic: G.08. Drugs of Abuse and Addiction

Title: A transgenic mouse overexpressing a circadian clock-related gene showed decreased locomotor sensitization and conditioned place preference toward methamphetamine

Authors: *M. KIM, J. DE LA PEÑA, I. DELA PEÑA, C. BOTANAS, R. CUSTODIO, K. YOU, T. WOO, J. CHEONG, H. KIM
Uimyung Reasearch Inst. For Neurosci., SEOUL, Korea, Republic of

Abstract: Abstract

Drug addiction is a chronic and relapsing brain disorder characterized by compulsive drug seeking and use, despite harmful consequences. The number of the drug abusers is continuously increasing worldwide. The mechanism underlying drug addiction is still poorly understood and is thought to be affected by complex interactions of endogenous and exogenous factors. Efforts to understand the nature of addiction in humans face various ethical limitations. Transgenic animal models have emerged as useful tools in understanding the genetic underpinnings of drug addiction and in discovering potentials treatment strategies. In our previous study, we have identified candidate genes that might be associated with addiction to psychostimulants. Based on this finding, we generated a transgenic (TG) animal model overexpressing one of the candidate genes, which is related to the circadian clock. We then investigated the rewarding effects of

methamphetamine (METH) in this TG mouse through the conditioned place preference (CPP) test. We also assessed the locomotor sensitization response of this TG mouse to repeated (7 days) METH administration and METH challenge after a period of abstinence. In addition, we investigated the expression levels of dopamine-related genes in the striatum and PFC of the TG mouse. We have found that TG mice showed lesser rewarding effects to METH in the CPP test than wildtype mice. They also demonstrated decreased locomotor sensitization response to repeated METH treatment and METH challenge. These results suggest that the TG mouse is less sensitive to the addictive effects of METH. We have also found that the baseline expression level of MAOa, an enzyme that metabolizes dopamine, is increased in the striatum and PFC of the TG mouse. Taken together, the gene of interest might have a protective role against the addictive effects of METH and that this effect is probably mediated, in part, by an increased dopamine metabolism in the brain. Additional studies are underway to assess the response of the TG mouse to other addictive drugs and characterize further the mechanisms behind the present findings.

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Poster

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Title: Alcohol cue-activated neurons in the nucleus accumbens core mediate the "incubation" of alcohol seeking: Neuronal ensemble-specific gene expression profiling via FACS and RNA-seq

Authors: *G. DE NESS[1], ***G. DE NESS**[1], A. LAQUE[1], V. REPUNTE-CANONIGO[1], G. E. WAGNER[1], T. KERR[1], D. WATRY[1], M. R. MAYFORD[2], B. T. HOPE[3], P. P. SANNA[1], F. WEISS[1], N. SUTO[1]

[1]The Scripps Res. Inst., La Jolla, CA; [2]Psychiatry, Univ. of California San Diego, La Jolla, CA; [3]Behav Neurosci, NIH/NIDA, Baltimore, MD

Abstract: As is the case for alcohol seeking in recovering alcoholics, alcohol seeking in animals progressively intensifies during protracted abstinence. The brain mechanisms responsible for this behavioral maladaptation or “incubation” are not yet known. Given that the nucleus accumbens (NAc) plays a major role in alcohol seeking, we hypothesized that neural activity in this site contributes to the incubation of alcohol seeking. Wistar rats were trained to lever-press for alcohol paired with a light cue. Alcohol sessions were then discontinued and the rats were tested for alcohol seeking on the first and fourteenth days of abstinence (D1 & D14) under an extinction condition. Lever pressing for the light-cue (alcohol cue) significantly increased over abstinence accompanied by a similarly time-dependent increase in neural activity, as indicated by a greater number of neurons expressing the activity marker Fos, in NAc core and shell. However, basal lever pressing on D1 was associated with a significant Fos expression in NAc core but not shell - suggesting that neural activity in NAc core, rather than shell, drives alcohol seeking. We therefore next determined the effects of selective disruption of alcohol cue-activated neurons in NAc core on (1) execution and (2) incubation of alcohol seeking. For this, male Fos-lacZ transgenic rats were trained as the Wistar rats but tested for alcohol seeking on the first, third and fourteenth days of abstinence (D1, D3 & D14). Daun02 or vehicle was injected into NAc core following the D1 test. In Fos-lacZ rats, Daun02 (prodrug) is converted into daunorubicin (cytotoxin) only in Fos+ activated neurons, thereby inducing selective apoptosis. Daun02 disruption of alcohol cue-activated neurons on D1 spared the basal expression (evident on D3) but blocked the intensification (evident on D14) of lever pressing - indicating that incubation rather than execution of alcohol seeking requires such a functional unit of neurons (neural ensembles) in NAc core. We next aim to determine time-dependent changes in transcriptional profile unique to these ensembles via FACS and RNA-seq. The results are expected to reveal neuroadaptation functionally linked to the behavioral maladaptation manifesting as incubation of alcohol craving.

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Poster

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Program#/Poster#: 075.17/MM15

Topic: G.08. Drugs of Abuse and Addiction

Support: F31-DA042514

DP1-DA039650

R00-DA034681

Title: Identification and manipulation of dopamine-mediated transcriptional and epigenetic dynamics in rat striatal cultures

Authors: *K. E. SAVELL, F. SULTAN, J. S. REVANNA, J. J. DAY
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Abstract: Drug addiction is a chronic, relapsing disorder in which drug-related associations are capable of exerting tremendous control over behavior long after drug consumption has ceased. Drugs of abuse cause long-lasting functional and structural alterations in the brain's reward circuits. All drugs of abuse increase dopamine concentrations in the nucleus accumbens (NAc), a key reward structure that integrates contextual and cue-related information and regulates motivated behavior. Recent work has proposed that epigenetic modifications, such as DNA methylation, contribute to cocaine-induced plasticity in the NAc. Moreover, novel findings reveal that drugs of abuse induce epigenetic changes in the NAc and that these changes control cocaine-related neuroadaptations. However, very little is known about how specific epigenetic modifications at individual genes implicated in addiction affect the reward circuit. To model dopamine elevations that occur in the NAc with use of drugs of abuse, we treated cultured rat striatal neurons with doses of dopamine that mimic concentrations similar to *in vivo* cocaine administration. We performed RNA-sequencing and reduced representation bisulfite sequencing to characterize how dopamine signaling alters gene expression and DNA methylation patterns across the genome. Based on these results and *in vivo* datasets, we utilized CRISPR-dCas9 methods to alter DNA methylation status at individual genes to understand the causal relationship between DNA methylation changes and gene expression. Promoter hypermethylation at genes found to be altered by dopamine and cocaine was capable of producing robust and enduring silencing of gene expression. The persisting alterations that occur after exposure to drugs of abuse are believed to drive pathological drug seeking and relapse long after drug use has ceased. Our results suggest that altering DNA methylation states at addiction-linked genes may provide a potential way to target long-lasting gene expression patterns induced by drugs of abuse.

Disclosures: K.E. Savell: None. **F. Sultan:** None. **J.S. Revanna:** None. **J.J. Day:** None.

Poster

075. Addiction Genetics

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 075.18/MM16

Topic: G.08. Drugs of Abuse and Addiction

Title: Gene network of dopamine receptor type 2 (Drd2) in addiction

Authors: *L. GUERRI[1], L. DOBBS[2], A. BADILLO MARTINEZ[1], V. ALVAREZ[2], D. GOLDMAN[1]
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Abstract: Low availability of type-2 dopamine receptors (D2Rs) in the striatum has been observed in a wide range of conditions associated with impaired decision-making, such as addiction, obesity and ADHD. Two neuronal populations account for most of D2R expression in the striatum: Medium Spiny Neurons of the “indirect pathway” (iMSNs) and the projections (auto-receptors) of dopamine neurons from VTA. However, neither the causes, the functional consequences nor the cellular component of this downregulation are well understood. To study the downstream effects of D2R gene (Drd2) downregulation and its gene network, we purify the whole transcriptome of iMSNs in male and female mice with either WT (wt) or low (het) level of Drd2 expression. This is achieved by conditionally driving both the expression of the Translating Ribosome Affinity Purification (TRAP) system and a floxed Drd2, in iMSNs. RNAseq analysis of a subset of samples shows a strong enrichment of known iMSN markers in the TRAP positive fraction and corresponding depletion in the negative fraction. Further, the TRAP negative fraction shows enrichment of transcripts characteristic of other striatal neurons and glial cells, allowing for their study in parallel. Preliminary analysis of positive fractions in Drd2 wt and het shows the differential expression of interesting genes related to neurotransmitter regulation and signaling molecules among others. Comparison of the four groups: Drd2 wt and het in males and females, will allow us to identify the gene network that is affected by Drd2 downregulation in addiction. These groups will be further studied in the context of cocaine exposure and self-administration paradigm. A full set of samples from untreated mice are currently being sequenced. The results for the complete analysis will be delivered at poster presentation.

Disclosures: L. Guerri: None. **L. Dobbs:** None. **A. Badillo Martinez:** None. **V. Alvarez:** None. **D. Goldman:** None.

Poster

075. Addiction Genetics

Location: Halls A-C

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Program#/Poster#: 075.19/MM17

Topic: G.08. Drugs of Abuse and Addiction

Support: MEXT KAKENHI Grant Number 16K08913

Title: Comparison of microRNAs expression between ethanol and methamphetamine dependence

Authors: *K. MIZUO, S. WATANABE
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Abstract: Recent studies demonstrated that microRNA (miR) have important role in the regulation of several nervous functions. We previously reported that acute ethanol administration caused the long-lasting increase in the expression of miR-124 in mouse brain. In the present study, we investigated the expression of miRs in mouse ethanol and methampetamine dependence. Mice were treated with liquid diet containing ethanol for 10 days. Using the escalating ethanol dosage schedule, the mice were fed the ethanol diet as follows: 1st day: 1 w/v%; 2nd and 3rd day: 3 w/v%; 4th to 10th day: 4 w/v% ethanol diet, respectively. The control mice were given the same volume of ethanol-free liquid diet with sucrose substituted in isocaloric quantities for ethanol. Methamphetamine dependence was evaluated by conditioned place preference. The mice chronically treated with ethanol revealed severe withdrawal signs after discontinuation of ethanol. The mice were killed by decapitation and the limbic forebrain (containing nucleus accumbens) was dissected. RT-PCR analysis for detection of miRs in the brain was performed. We observed that the expression of brain-enriched miR-124 was significantly increased in limbic forebrain following chronic treatment of ethanol. The expression of miR-124 was also increased in limbic forebrain of methamphetamine-dependent mice. It has been reported that miR-124 play a critical role in the dependence of cocaine. These findings suggest that the miR-124 is a common miR in the regulation of dependence of abused drugs. On the other hand, the expression of miR-146a was significantly increased in ethanol dependence whereas no change in the expression was observed in methamphetamine dependence. In conclusion, we clarified that miR-124 may play role in dependence of abused drugs. Furthermore, the present study suggests that the changes in the expression of miR-146a is specific in the ethanol dependence.

Disclosures: K. Mizuo: None. **S. Watanabe:** None.

Poster

075. Addiction Genetics

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA037738

NIH Training Grant 4T32 DA007097-35

Engdahl Family Foundation Grant

Title: Repetitive morphine administration induces sex-dependent transcriptomic changes in the adult rat nucleus accumbens

Authors: *M. S. GADES[1], K. JEONG[1], A. C. HARRIS[1], P. V. TRAN[2], J. C. GEWIRTZ[1]
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Abstract: Sex differences in vulnerability to and patterns of drug abuse may in part be associated with differential epigenetic modifications that occur during early drug use. In a preliminary study, we have employed next generation RNA sequencing (NGS) to comprehensively identify differential gene expression in the nucleus accumbens following experimenter-administered morphine administration in male and female rats. Adult rats were injected daily with either morphine (5mg/kg) or saline for 10 days. RNA was extracted from the nucleus accumbens and sequenced using Illumina HiSeq 2500. NGS data were processed using TopHat and Cufflinks packages through the Minnesota Supercomputing Institute. Transcripts from approximately 17,000 loci were sequenced with a false discovery rate < 0.05. Among these, morphine administration resulted in 58 and 49 differentially expressed genes in male and female rats, respectively. Moreover, only five of these genes overlapped between the two sexes. Further analysis of differentially expressed genes using the knowledge-based Ingenuity Pathway Analysis (IPA) software package highlights potentially altered protein synthesis and GABA signaling in males, and altered dopamine and glutamate signaling in females. Collectively, these preliminary findings demonstrate that daily morphine administration alters gene expression in the nucleus accumbens, and that these changes are sex-specific, suggesting potential molecular mechanisms underlying sex-differences in vulnerability to drug abuse. In addition to validating these initial findings, on-going experiments are investigating whether similar differential transcriptional effects are observed following response-contingent morphine administration (self-administration) and whether these changes involve epigenetic modification.

Disclosures: M.S. Gades: None. **K. Jeong:** None. **A.C. Harris:** None. **P.V. Tran:** None. **J.C. Gewirtz:** None.

Poster

076. Alcohol-Related Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 076.01/MM19

Topic: G.08. Drugs of Abuse and Addiction

Title: Chemogenetic activation of ventral tegmental area GABA neurons disrupts the timing of responding during ethanol self-administration

Authors: *A. K. SHIELDS[1], K. T. WAKABAYASHI[2], K. A. HAUSKNECHT[3], R.-Y. SHEN[4], S. HAJ-DAHMANE[5], A. VENNER[6], P. M. FULLER[7], C. E. BASS[8]

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Abstract: The ventral tegmental area (VTA) is a heterogeneous structure that plays a critical role in reward-seeking. The VTA is composed primarily of dopamine (~75%) and GABA (~25%) neurons, and although ethanol's reinforcing effects occur in part through interactions at GABA receptors, few studies have functionally evaluated how VTA GABA neuron activity influences ethanol seeking behavior. Recently we have developed an adeno-associated viral (AAV) approach to restrict expression of designer receptors exclusively activated by designer drugs (DREADDs) to GABA neurons in the VTA in wildtype rats. In the current study, we sought to determine how VTA-GABA neurons regulate ethanol-seeking behaviors in ethanol self-administration models. Rats were trained to press a lever to self-administer ethanol administered in a gelatin matrix under either continuous reinforcement (fixed ratio 1, FR1) or progressive ratio (PR) schedules, during a 6-hr session. While FR1 requires minimal effort, PR response requirements increase exponentially for each reward obtained. We hypothesized that activating VTA GABA neurons would disrupt responding for ethanol. The DREADD ligand, clozapine n-oxide (CNO, 0.3 mg/kg, i.p.), induced in a profound change in the response pattern under both schedules of reinforcement. Specifically, for plain gelatin and gelatin/ethanol mixtures (2.5, 5, and 10%), activation of VTA GABA neurons decreased the number of bouts (response interval < 20 min) and inter-bout intervals, however, bout length increased, often resulting in one long "linear" bout of responding over six hours. To evaluate this effect further, we also examined how activation of GABA neurons altered locomotion in an open-field. Additionally, we directly assessed if VTA-GABA activation altered reward-seeking by disrupting the perception of time and the timing of responses by using a Fixed Interval (FI) schedule of reinforcement. Together, these data indicate that VTA-GABA neurons influence reward- and ethanol-seeking behaviors possibly by multiple mesolimbic based effects on motivation and ability to respond.

Disclosures: A.K. Shields: None. **K.T. Wakabayashi:** None. **K.A. Hausknecht:** None. **R. Shen:** None. **S. Haj-Dahmane:** None. **A. Venner:** None. **P.M. Fuller:** None. **C.E. Bass:** None.

Poster

076. Alcohol-Related Behavior

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Program#/Poster#: 076.02/MM20

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA024112

Title: Ventral tegmental area GABA neurons influence motivation and effort to obtain sugar and ethanol mixtures

Authors: *K. T. WAKABAYASHI[1], A. SHIELDS[2], R. BHIMANI[4], J. PARK[3], K. A. HAUSKNECHT[6], R.-Y. SHEN[5], S. HAJ-DAHMANE[7], A. VENNER[8], P. M. FULLER[9], C. E. BASS[10]
[1]Res. Inst. On Addictions / Univ. At Buffalo, Buffalo, NY; [2]Univ. At Buffalo, Amherst, NY; [3]Univ. At Buffalo, Buffalo, NY; [4]Univ. at Buffalo, Amherst, NY; [5]Res. Inst. on Addictions, Univ. at Buffalo, Buffalo, NY; [6]Univ. Buffalo, SUNY, Buffalo, NY; [7]Univ. at Buffalo - The State Univ. of New York, Buffalo, NY; [8]Dept. of Neurol., [9]Harvard Med. Sch., Boston, MA; [10]3435 Main St., Univ. At Buffalo SUNY, Buffalo, NY

Abstract: The mesolimbic system is a well-studied brain circuit that modulates multiple motivated behaviors. In this circuit, dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) regulate reward-seeking processes related to the effort and cost required to obtain a natural or alcohol reward. Yet the VTA also contains other neurons, including GABA, whose contribution to reward-seeking is less understood. We hypothesize that VTA-GABA neurons inhibit mesolimbic DA, influencing the effort-cost calculation when seeking either sucrose sugar or alcohol rewards. To test this hypothesis, we targeted VTA-GABA neurons with adeno-associated viruses (AAVs) that restrict expression of activating Designer Receptor Exclusively Activated by Designer Drugs (DREADDs, hM3D) to these neurons. Rats were then tested in models of alcohol or sucrose reward-seeking under two different “effort” conditions; one where the effort to gain a reward was minimal (either “free access” to sucrose or under a continuous reinforcement schedule (FR1) for ethanol), and one under a condition where the needed effort increased exponentially after each reward (PR, progressive ratio). Stimulation of VTA-GABA neurons with clozapine n-oxide (CNO, 0.3 mg/kg) during free access/FR1, and during PR for either reward, produced a marked shift in the pattern of responding used to obtain the reward during these tasks, suggesting that VTA-GABA neurons may play a key role in effort calculation for both natural and ethanol reward. Interestingly, alcohol is often drank with sweeteners to make it more palatable. Understanding the neural mechanisms that contribute to the synergistic potential of ethanol and sugar consumption is complicated by the fact that some sugars are centrally active (i.e. glucose) and can directly interact with glucose-sensitive (e.g. melanin concentrating hormone, MCH) neurons. MCH neurons have previously been shown to interface with the mesolimbic system and influence alcohol consummatory behavior suggesting MCH-NAc projections may represent a neural mechanism underlying the interactions between ethanol and sugar consumption behaviors. Initial data exploring the potential of glucose sugars to potentiate ethanol consumption as opposed to equally caloric but centrally inactive sugars, such as fructose, will be discussed.

Disclosures: K.T. Wakabayashi: None. **A. Shields:** None. **R. Bhimani:** None. **J. Park:** None. **K.A. Hausknecht:** None. **R. Shen:** None. **S. Haj-Dahmane:** None. **A. Venner:** None. **P.M. Fuller:** None. **C.E. Bass:** None.

Poster

076. Alcohol-Related Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 076.03/MM21

Topic: G.08. Drugs of Abuse and Addiction

Support: Hubert and Richard Hanlon Trust

Title: Neuronal numbers in the ventral tegmental area and the nucleus accumbens in alcohol preferring and non-preferring rats

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[1]Doisy Hlth. Sciences: Office of Occup. Therapy, St. Louis Univ., Saint Louis, MO; [2]Occup. Sci. and Occup. Therapy, St. Louis Univ., St. Louis, MO

Abstract: Stereological examination of the mesocortical dopamine system in alcohol preferring , non preferring and control Wistar RatsThe mesocortical dopamine pathways are an important part of reward pathways in the brain. The Ventral tegmental area (VTA) and the nucleus accumbens (NA) may mediate the reward perception in ETOH abuse and may regulate non-preferring behavior. To this point, there have been few studies using design-based, non-mathematically biased stereological examinations in this model. Immunohistochemical preparation of the tissue used tyrosine hydroxylase and a thionine counter stain on 30 age matched animals: males and females, ETOH Preferring (AP) vs. ETOH Non-Preferring (NP) vs. Wistar controls. In our first analysis, the volume of the nucleus accumbens with Cavalieri point counting method which yielded a significant increase of size with the ETOH non-preferring versus the controls and the ETOH preferring rats. The second analysis uses the dissector method for number and isoropic uniform random (IUR) design for cell body volume in the VTA of all groups which yielded increased number for ETOH preferring versus the non-preferring and controls. We determined an increase in cell body volume for the ETOH non-preferring versus the ETOH preferring and controls.

Disclosures: S.O. Ahmad: None. **G. Caponera:** None.

Poster

076. Alcohol-Related Behavior

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH intramural funding ZIA-AA000218

Title: The role of ghrelin signaling in modulating behavioral and neural correlates of alcohol use disorder: A human laboratory study with exogenous ghrelin

Authors: *M. FAROKHNIA[1], E. N. GRODIN[1], M. R. LEE[1], E. N. OOT[1], A. N. BLACKBURN[1], B. L. STANGL[1], M. L. SCHWANDT[1], L. A. FARINELLI[1], R. MOMENAN[1], V. RAMCHANDANI[1], L. LEGGIO[1,2]
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Abstract: Background: Gut-brain axis represents a promising, yet under-explored research domain in understanding the underlying neurobiology of alcohol use disorder. Ghrelin, a peptide primarily synthesized by endocrine cells of the stomach, has been shown to modulate both central reward and stress pathways. In rodents, ghrelin injection enhances motivation for alcohol; human studies also suggest a positive relationship between endogenous ghrelin levels and alcohol craving. However, whether and how ghrelin signaling may affect alcohol-seeking behavior in humans remains unknown. **Methods:** This was a randomized, crossover, double-blind, placebo-controlled, human laboratory study. Participants were non-treatment seeking alcohol-dependent heavy-drinking individuals. A 10-minute loading dose of intravenous ghrelin (3 mcg/kg) followed by a continuous ghrelin infusion (16.9 ng/kg/min) was administered. *Intravenous alcohol self-administration (IV-ASA) experiment*: Participants were given the opportunity to press a button to receive alcohol infusions using the Computerized Alcohol Infusion System with a progressive ratio schedule. Each infusion raised the blood alcohol concentration by 7.5 mg% over 2.5 minutes followed by a decrease of 0.5 mg% per minute until the next infusion. *Brain functional magnetic resonance imaging (fMRI) experiment*: Scans were performed while beverage, food, and neutral cues were presented indicating participants' chance to win alcohol, snacks, and no rewards in proportion to their success in hitting the targets. Resting-state brain scans were also acquired. **Results:** Participants self-administered higher number of alcohol infusions during the ghrelin than placebo session (percent change: 24.97±10.65, p=0.04, Cohen's d=0.74). They also started pressing the button sooner (p=0.01) and received their first infusion earlier (p=0.03) during the ghrelin session. Intravenous ghrelin increased left amygdala response to alcohol cues (p=0.01), and respectively decreased and increased right medial orbitofrontal cortex (p=0.01) and left nucleus accumbens (p=0.08) response to food cues. Ghrelin also decreased the resting-state functional connectivity between right amygdala and right medial orbitofrontal cortex (p=0.06). **Conclusion:** This study represents the first human evidence that exogenous ghrelin administration modulates both behavioral and neurobiological correlates of alcohol-seeking behavior, providing rationale for studying manipulation of the ghrelin system as a novel treatment approach for alcohol use disorder.

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Poster

076. Alcohol-Related Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 076.05/NN1

Topic: G.08. Drugs of Abuse and Addiction

Title: Selective effects of chemogenetic inhibition of orbitofrontal cortex on operant ethanol seeking

Authors: *J. HERNANDEZ[1], A. BINETTE[1], D. E. MOORMAN[2]
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Abstract: Orbitofrontal cortex (OFC) activity is associated with reward valuation, preference and seeking. Despite a growing consensus that the OFC may be disrupted in addiction, few studies have examined the role of the OFC in alcohol use, particularly during operant alcohol seeking. To address this issue, we used inhibitory DREADDs to inhibit OFC neuronal activity during alcohol and sucrose seeking tasks.
12 male and 12 female Wistar rats received homecage intermittent access to 20% ethanol for 4 weeks. We then stereotaxically injected 650 nl of AAV8-hSyn-hM4Di-mCherry bilaterally into the OFC. Rats were then trained on a cue-driven ethanol/sucrose seeking task. A nosepoke triggered one of three reward-predicting tones: 20% ethanol (1 kHz), 10% ethanol (10 kHz), or sucrose (5 kHz). Rats were required to leave the nosepoke and enter the reward port in less than 4 s to retrieve the reward. Rats performed two session types: blocked and interleaved trials. In blocked trial sessions, only one type of tone and reward was presented (10% ethanol, 20% ethanol, or sucrose). In interleaved sessions, two separate tones/reward trials (e.g., 20% ethanol and sucrose) were randomly interleaved.
Rats displayed individual variability in home cage ethanol consumption. During the last drinking session, mean ethanol consumption was 3.15 g/kg/24-hrs for low drinking rats and 3.97 g/kg/24-hrs for high drinking rats. During blocked sessions, rats performed the greatest number of rewarded trials for sucrose, followed by 10% ethanol and 20% ethanol. CNO treatment (3 mg/kg, i.p.) decreased the number of rewarded trials for 10% ethanol in both low and high-drinking rats, but did not significantly alter sucrose or 20% ethanol seeking. During interleaved sessions, CNO treatment had no significant effect on the number of rewarded trials performed. In a subset of animals, EtOH seeking after OFC inactivation was enhanced in low-preferrers and decreased in high-preferrers. Due to the heterogeneous group interactions (male/female x low-/high-preferrer), more studies, currently underway are necessary to clarify these results. These preliminary data suggest that the OFC may preferentially encode the value of 10%, but not 20% ethanol. The results also hint at a hierarchical encoding of preference by OFC whereby selective preference (e.g., in high- vs. low-preferrers) is differentially modulated by OFC function.

Disclosures: **J. Hernandez:** None. **A. Binette:** None. **D.E. Moorman:** None.

Poster

076. Alcohol-Related Behavior

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Topic: G.08. Drugs of Abuse and Addiction

Support: PNSD001I2015 from National Plan on Drug abuse, Ministerio de Sanidad of Spain

NIH AA016654

AA020912

Title: Receptor protein tyrosine phosphatase β/ζ modulates alcohol-induced behavioral responses

Authors: R. FERNÁNDEZ-CALLE[1], *E. GRAMAGE[1], M. VICENTE-RODRÍGUEZ[1], C. PÉREZ-GARCÍA[1], J. M. ZAPICO[1], C. CODERCH[1], M. PASTOR[1], B. DI GERONIMO[1], B. DE PASCUAL-TERESA[1], A. RAMOS[1], A. W. LASEK[2], G. HERRADÓN[1]
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Abstract: Pleiotrophin (PTN) is a neurotrophic factor that is upregulated in the prefrontal cortex after alcohol administration. Pleiotrophin knockout (Ptn-/-) mice are more vulnerable to the rewarding effects of ethanol whereas the sedative effects of alcohol are reduced and its conditioning effects completely blocked in mice with PTN transgenic overexpression in the brain. PTN is the endogenous ligand for Receptor Protein Tyrosine Phosphatase (RPTP) β/ζ (a.k.a. PTPRZ1, RPTPβ, PTPζ) and inhibits its phosphatase activity, suggesting an important role of this phosphatase in the regulation of alcohol effects. To test this hypothesis, we developed small-molecule inhibitors of RPTP β/ζ (MY10, MY33-3) and tested them for ethanol-induced activation of signaling pathways in vitro and in conditioned place preference (CPP) and binge-like drinking models in vivo. We found that ethanol treatment of neuroblastoma cells rapidly increased phosphorylation of anaplastic lymphoma kinase (ALK) and TrkA, known substrates of RPTP β/ζ. Treatment of neuroblastoma cells with MY10 or MY33-3 also increased levels of phosphorylated ALK and TrkA. However, concomitant treatment of neuroblastoma cells with ethanol and MY10 or MY33-3 blocked the increase in the phosphorylation of TrkA and ALK. To determine if inhibition of RPTP β/ζ regulates ethanol consumption, we treated mice with MY10 or MY33-3 before testing them for binge-like drinking using the drinking in the dark protocol. Mice treated with RPTP β/ζ inhibitors drank less ethanol than controls. In addition, MY10 treatment reduced alcohol-induced conditioned place preference. These results demonstrate for the first time that ethanol engages TrkA signaling and that RPTP β/ζ modulates the signaling pathways activated by alcohol and the behavioral responses to this drug. The data

support the possibility that RPTP β/ζ might be a novel target of pharmacotherapy for reducing excessive alcohol consumption. *Supported by PNSD001I2015 from Plan Nacional Sobre Drogas, Ministerio de Sanidad, Servicios Sociales e Igualdad of Spain (to GH) and NIH AA016654 and AA020912 (to AWL).*

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Poster

076. Alcohol-Related Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 076.07/NN3

Topic: G.08. Drugs of Abuse and Addiction

Title: Hedonic and aversive taste reactions to ethanol vary between differentially reared rats as a function of ethanol concentration

Authors: *T. J. WUKITSCH, E. C. BRASE, M. S. BLOEDEL, M. E. CAIN
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Abstract: Isolation rearing increases operant responding for ethanol (ETOH) (Deehan et al., 2007). However, the aspects of motivation that drives the increased responding for ETOH between differentially reared rats is unknown. While a large body of literature has looked at drug addiction through the lens of “wanting” alone or combined with the “liking” of the substance, limited research has explored how differential rearing alters liking (hedonic value) (Robinson & Berridge, 2008). Understanding differences in “liking” between differentially reared rats will aid in understanding motivational factors involved in ETOH addiction vulnerability. In the current study, we assessed differences in both hedonic and aversive responding to ETOH between differentially reared animals using taste reactivity. We hypothesized that isolated rats would have higher amounts of hedonic behaviors (e.g. tongue protrusions, mouth movements) and lower amounts of aversive behaviors (e.g. gapes, fluid expulsions) across a range of ETOH concentrations compared to SC rats. Male Sprague Dawley rats arrived in the lab on postnatal day (PND) 21 and were randomly assigned to either the isolated (IC) or standard condition (SC) for a 30 day rearing period. Rats were then implanted with intraoral fistulas which were routed from the mouth to a metal connector protruding from an acrylic head cap anchored to the skull. After recovery, rats underwent taste reactivity testing for a range of ETOH concentrations presented in a counterbalanced order (H2O; 5%, 10%, 20%, 30%, & 40% ETOH). Videos were scored frame by frame starting with the first mouth movement according to the standards put forth by Grill and Norgren (1978). Preliminary results from hedonic and aversive behavioral

count totals show trends suggesting that both hedonic and aversive responding between differentially reared animals vary as a function of ETOH concentration. The initial results suggest that at higher ETOH concentrations (40%) IC rats have more aversive responses than SC rats while at lower ETOH concentrations (5%) SCs rats have more hedonic responses than IC rats. These results suggest that differential rearing may alter sensitivity to the taste of alcohol resulting in motivational differences to acquire alcohol in operant paradigms.

Disclosures: T.J. Wukitsch: None. **E.C. Brase:** None. **M.S. Bloedel:** None. **M.E. Cain:** None.

Poster

076. Alcohol-Related Behavior

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Topic: G.08. Drugs of Abuse and Addiction

Support: Murdock Trust

Title: Accumbal ghrelin and glucagon-like peptide 1 modulation of ethanol reward and ingestive behavior in female rats

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Abstract: Increasing evidence suggests that ghrelinergic and glucagon-like peptide 1 (GLP-1) signaling interact in the hypothalamic regulation of energy substrate utilization and recent work indicates that these peptides individually play a role in the control of ethanol reward and dependence. Furthermore, female rodents tend to consume more alcohol and work harder for access than males, particularly during the metestrus and diestrus phases of the estrous cycle. In the present study, we investigated the potential interaction between ghrelin and GLP-1 in the mesolimbic reward pathway in ethanol dependent female rats. Animals were habituated to ethanol over the course of twelve weeks in a two bottle paradigm and unilaterally cannulated in the nucleus accumbens core or shell. Our results indicated that ghrelin and GLP-1 interact within the accumbens core and shell to regulate ethanol consumption and ingestive behavior in a regionally distinct manner. In particular, our data provide compelling evidence that ghrelin and GLP-1 may be part of different reward and food intake circuits in the core, but part of the same reward circuit within the shell. Estrous-dependent effects were found in measures of water and total fluid intake, but not ethanol or food intake, suggesting that the reason female rats drink more during the metestrus and diestrus stages of the estrous cycle may be due to sex differences in fluid homeostasis neurophysiology as opposed to reward signaling.

Disclosures: S. Abtahi: None. **E. Howell:** None. **P.J. Currie:** None.

Poster

076. Alcohol-Related Behavior

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 076.09/NN5

Topic: G.08. Drugs of Abuse and Addiction

Support: AA023648

AA022082

Title: Stimuli conditioned to EtOH availability during withdrawal produce compulsive-like behavior in tests of EtOH seeking as measured by resistance to punishment and tolerance of increased workload

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Abstract: Alcoholism is a chronically relapsing disorder characterized by compulsive ethanol (EtOH) seeking and use. One major factor implicated in vulnerability to relapse includes learned responses induced by contextual stimuli that have become associated with the subjective actions of EtOH. In alcoholics, the severity of EtOH craving evoked by environmental cues is highly correlated with the degree and history of EtOH dependence. This is hypothesized to be, in part, due to experiences of EtOH during withdrawal, which modifies the individual's reinforcement history to include the subjective effects of EtOH during this state, consequently enhancing EtOH's reinforcing actions. We have previously shown that environmental cues conditioned to EtOH availability during withdrawal produces significant reinstatement and that in animals with such a conditioning history, stimuli conditioned to EtOH availability in the nondependent state lose their efficacy to elicit EtOH seeking. Here, we extend our previous findings by examining the role of withdrawal-related conditioning on EtOH seeking and vulnerability to relapse using two models of drug compulsion. First, we tested whether reinstatement of EtOH seeking induced by cues conditioned to EtOH availability during withdrawal facilitate willingness to "work more" in anticipation for EtOH, as measured by increasing FR ratios for presentation of an EtOH-associated stimulus. Second, we examined whether responding elicited by stimuli conditioned to EtOH availability during withdrawal is resistant to punishment, compared to the effects of stimuli associated with EtOH in nondependent states. The results show that stimuli conditioned to EtOH availability during withdrawal, unlike stimuli conditioned in the nondependent states, evoke compulsive-like EtOH seeking, as shown by rats' willingness to expend greater effort to obtain EtOH and resistance to suppression of cue-induced responding despite adverse consequences.

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Poster

076. Alcohol-Related Behavior

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Using taste reactivity to study neural systems underlying alcohol preference in behaving rats

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Abstract: Understanding the neural basis of alcohol preference, and its impact on alcohol use disorders, is important for potential treatment development. Like humans, rats have individual preferences for ethanol (EtOH) and can be categorized as low or high drinkers after 2-4 weeks of homecage intermittent EtOH access. Most studies of the neural basis of EtOH motivation focus on preferring rats, largely because non-preferring rats do not actively seek EtOH. Neural circuits driving motivation for, or "wanting" a reinforcer, differ from those encoding reward palatability, or "liking" (e.g., K. Berridge et al.). It is unclear whether high- vs. low-preference for EtOH is driven by motivation, palatability, or some interaction. A clear dissociation of neural circuits underlying EtOH liking and wanting may provide critical information regarding which neural systems are disrupted in dependence.

We have adapted intraoral taste-reactivity techniques to passively deliver EtOH intraorally in freely-moving rats. Our work is inspired by previous studies of intraoral EtOH infusion by Kiefer and colleagues, and others, and is modeled on recent taste-reactivity studies by Katz, Fontanini, Samuelsen, and colleagues. Following four weeks homecage intermittent access to 20% EtOH, rats are implanted with an intraoral polyethylene cannula. During behavioral testing, intraoral cannulae are connected to a manifold of at least four polyimide tubes, each of which are connected to a pump delivering a separate tastant. Rats are presented with separate tone cues which predict the delivery of ~80ul of 20% EtOH, sucrose, or quinine. A separate channel delivers water to wash out tastants between deliveries. Using video and EMG, we measure taste reactivity based on canonical hedonic responses (e.g., licks for palatable and gapes for unpalatable infusions).

With these intraoral cannula systems, we can characterize relative preference for EtOH in each individual rat by comparing oromotor responses to ethanol vs. sucrose and quinine in a single session. These results are compared to homecage drinking and operant self-administration to

create a multidimensional behavioral profile for each individual animal, describing its integrative degree of “liking” and “wanting” alcohol. Current preliminary results in 8 male Wistar rats indicate a correlation between homecage EtOH drinking and taste reactivity. The results of these behavioral studies will be presented along with neural activation measures (Fos and in vivo electrophysiological recordings) to characterize neural correlates of EtOH liking and wanting in high- and low-preferring individuals.

Disclosures: S.M. Rios: None. **B. Kaminska:** None. **D.E. Moorman:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH NIAAA AA007702

Title: Caffeine place conditioning in male dba/2j mice

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Abstract: Caffeine is a mild psychostimulant heavily used throughout the world primarily for its ability to promote wakefulness through its actions on the adenosine system in the central nervous system. Using rodent models, previous studies have shown that caffeine has a biphasic effect, with lower doses producing conditioned place preference (CPP), while higher doses produced conditioned place aversion (CPA). Recently, given the increase in the use of caffeine in combination with alcohol, studies have begun investigating the rewarding effects of this combination using the conditioned place preference procedure. However, these studies have produced mixed results, potentially due to procedural variations between studies (i.e., trial duration, apparatus, cue type). Previous work in our lab has shown that the duration of a conditioning trial can significantly affect the strength of CPP. Indeed, CPP induced by ethanol was inversely related to trial duration. The present study was designed to examine the effect of conditioning trial duration on caffeine-induced CPP and CPA. Adult male DBA/2J mice (n = 96) were randomly assigned to one of six groups in a factorial design that crossed trial duration (5, 30 or 60 min) with caffeine dose (3 or 30 mg/kg). Using an unbiased one-compartment training procedure, mice within each group were randomly assigned to receive caffeine paired with one of two tactile floor cues; the other floor cue was paired with saline. Mice were tested for floor preference without drug after the first 4 trials of each type and again after a total of 6 trials. We found that the high dose of caffeine induced CPA, particularly when paired with long conditioning sessions. Furthermore, our data suggested that the low dose of caffeine might be

rewarding when a short (5-min) trial duration is used. In addition, caffeine dose-dependently increased activity during conditioning, and mice exposed to longer conditioning sessions were more active than those exposed to shorter conditioning sessions. Together, these data demonstrate that the parameters used during caffeine-induced place conditioning may have important effects on activity and conditioned preference/aversion. Supported by AA007702.

Disclosures: A. Zuniga: None. **C.L. Cunningham:** None.

Poster

076. Alcohol-Related Behavior

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Topic: G.08. Drugs of Abuse and Addiction

Title: The Role of Synaptotagmin 1 in alcohol-related behaviors

Authors: *E. D. BARBIER[1], E. AUGIER[1], E. DOMI[1], R. BARCHIESI[1], G. AUGIER[1], C. R. WAHLESTEDT[2], M. HEILIG[1]
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Abstract: Alcohol use disorder is characterized by broad and persistent changes in gene expression. Although numerous candidate genes have been associated with alcohol addiction, the underlying neural adaptations are not well understood. Recently, we found that synaptotagmin 1 (SYT1) was down-regulated in the medial prefrontal cortex (mPFC) of alcohol post-dependent compared to non-dependent rats. SYT1 is a Ca^{2+} sensor in the membrane of the pre-synaptic axon terminal. It interacts with the synaptic protein of the SNARE complex to induce neurotransmitter exocytosis. Given the important role of SYT1 in neurotransmitter release, we hypothesized that SYT1 may participate to the dysregulation of the mPFC function observed in alcohol use disorder. To functionally assess the role of SYT1 in alcohol-related behaviors, we injected an adeno-associated viral (AAV) vector expressing a shRNA to *Syt1* in the mPFC. We found that downregulation of *Syt1* in the mPFC increased motivation to consume alcohol as indicated by an increase in both alcohol operant self-administration and breakpoint for alcohol. Rats with downregulation of *Syt1* also showed compulsive-like behaviors as indicated by a greater tolerance to quinine adulteration when increasing concentration of quinine were added to the alcohol solution. Altogether, these findings demonstrated that *syt1* downregulation is sufficient to mimic alcohol-related behaviors observed in alcohol post-dependent rats, suggesting that SYT1 may play an important role in motivation and compulsivity, two main features of alcohol addiction.

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Poster

076. Alcohol-Related Behavior

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Program#/Poster#: 076.13/NN9

Topic: G.08. Drugs of Abuse and Addiction

Title: The effects of combined alcohol and nicotine in a multi-bottle choice paradigm in C57BL/6J mice

Authors: *J. N. BERRY, O. I. AKINBO, B. W. L. DUKE
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Abstract: Alcohol and nicotine are both very commonly abused and are also widely abused in combination with one another. Smoking tobacco cigarettes has been shown to increase the number of alcoholic drinks per day and increase the chances of alcohol dependence. As both substances are known to individually elevate dopamine levels in the mesocorticolimbic reward system and also activate the hypothalamic-pituitary-adrenal (HPA) axis to release stress hormones known as glucocorticoids, including corticosterone in rodents. Using a multi-bottle choice paradigm, we investigated the effects of the acquisition, maintenance, and withdrawal from chronic, combined alcohol (5-20% v/v) and nicotine (10-40 μg/ml). Withdrawal behavior and plasma corticosterone levels were measured 24 hours after alcohol and nicotine were both removed. Mice exposed to alcohol, nicotine, or the combination of alcohol and nicotine exhibited increased anxiety-like behavior as evidenced by increased number of marbles buried during the withdrawal period compared to water controls in the marble burying task. Similarly, mice exposed to alcohol and/or nicotine had elevated levels of the rodent stress hormone corticosterone during the withdrawal period. Given the large number of individuals who are co-dependent on both alcohol and nicotine, future studies should continue to examine the effects of combined alcohol and nicotine.

Disclosures: **J.N. Berry:** None. **O.I. Akinbo:** None. **B.W.L. Duke:** None.

Poster

076. Alcohol-Related Behavior

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Topic: G.08. Drugs of Abuse and Addiction

Title: Co-administration of caffeine and taurine increases ethanol-induced locomotor activity in mice

Authors: *L. ULENIUS[1], S. LARSSON[1], L. ADERMARK[1], B. SÖDERPALM[1,2], M. ERICSON[1]
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Abstract: The consumption of alcohol mixed with energy drinks has become a growing trend during the last decade. However, there are reports showing that this mix is associated with risks, such as increased probability of binge drinking, alcohol-related harm and development of alcohol use disorder. What ingredients in the energy drinks that are responsible for these increased risks, and the mechanisms of action underlying the effects, are not clear. Caffeine has been suggested to be the major pharmacological active ingredient in energy drinks. However, another common ingredient, previously associated with the dopamine elevating properties of ethanol, is the endogenous amino acid taurine. Ethanol increases extracellular levels of taurine and we have previously proposed that this increase of taurine is required for ethanol-induced accumbal dopamine release. Therefore, the role of taurine as a pharmacological active ingredient in energy drinks and its interaction with ethanol and caffeine should be further investigated. In the present study locomotor activity in male mice, a dopamine dependent behavior, following systemic administration (i.p.) of ethanol (1.75, 2.5, 3.25 g/kg), caffeine (1, 5, 15, 30 mg/kg) or taurine (30, 60, 300, 600 mg/kg) alone or in combination was determined. We found that caffeine but not taurine increased the locomotor stimulatory effect of ethanol. We also found that co-administration of caffeine and taurine further enhanced the locomotor response to a moderate dose of ethanol. We conclude that co-administration of caffeine and taurine as well as caffeine alone increase ethanol-induced locomotion in mice. Based on the present study we suggest that joint systemic administration of caffeine and taurine enhances centrally mediated dopamine dependent effects of ethanol, a phenomenon that needs to be further investigated in depth.

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Poster

076. Alcohol-Related Behavior

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Topic: G.08. Drugs of Abuse and Addiction

Support: NSF Grant DMS-1045015

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Title: Sensitization and tolerance to various doses of ethanol in adolescent and adult DBA/2J mice

Authors: *S. D. DICKINSON[1], A. E. FREDRICKSON[2], S. H. LONGENBACH[2], B. L. WENANDE[2], K. ZIEGLER-GRAHAM[3]
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Abstract: According to the National Institute of Alcohol Abuse and Alcoholism, 8.7 million people ages 12-22 reported using alcohol in the last month, while another 5.3 million reported binge drinking. Furthermore, alcohol consumption during adolescence is associated with a higher likelihood of alcohol dependency in adulthood. Repeated alcohol exposure in rodents can model neurobehavioral changes that can also occur in humans, such as tolerance and sensitization. Previous research has shown that adolescent and adult mice show differential behavioral effects of repeated alcohol exposure (Doremus-Fitzwater and Spear, 2016; Holstein et al., 2011). The purpose of the present study was to examine the effect of low and high doses of alcohol on adolescent and adult mice over time, with particular interest on the development of tolerance and sensitization. Thirty-eight adolescent mice (3 weeks) and thirty-eight adult mice (8 weeks) were injected with 2 g/kg (low dose equivalent to moderate drinking) or 4 g/kg (high dose equivalent to binge drinking) of ethanol daily for 11 days. Behavioral response to the ethanol injection was measured through changes in activity levels of each mouse recorded over a 10 minute period immediately following ethanol injection. Activity levels were recorded as the number of photobeams broken by mouse movement. To better understand the effects of rising blood alcohol data were analyzed on a minute-by-minute basis in addition to overall data from the full 10 minutes. As expected, 2 g/kg ethanol increased locomotor activity, and sensitization developed to this effect. Interestingly, this effect developed more rapidly in adults than in adolescents, though the magnitude of sensitization was equivalent by day 11. Also as expected, the 4 g/kg dose increased activity in the first minutes and then produced a profound decrease in movement in both adult and adolescent mice. Over days, however, adolescents showed greater variability in their response to the high dose, especially during minutes 5-10. Analysis of activity levels during different minutes account for tolerance and sensitization effects that may be present during

different places in the blood alcohol curve. The neurobehavioral patterns modeled by the mice in this study can provide insight into how humans may be affected by repeated alcohol use, as well as the effects that this usage may have on developing, adolescent brains.

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Poster

076. Alcohol-Related Behavior

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NIAAA RO1 AA019793

Title: Partner's drinking status influences the maintenance of monogamous pair bonds in male prairie voles

Authors: *A. T. WALCOTT, A. RYABININ
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Abstract: Alcohol abuse can have devastating effects on human relationships. In agreement with these effects in humans, previous research in our laboratory has shown that alcohol consumption can lead to disruption of pair bond formation in socially monogamous prairie voles. However, a majority of human literature on this subject explores the effects alcohol has on relationships that have already been established. Specifically, previous epidemiological research has shown that a discrepancy in alcohol consumption within couples leads to higher divorce rates, compared to couples in which both spouses consume heavy but similar amounts of alcohol. It is important to develop an animal model to understand the biological underpinnings of alcohol's effects on established bonds to lead to better treatment and prevention alternatives. Therefore, the present study investigated whether a discrepancy in alcohol consumption in pair bonded male prairie voles, leads to a disruption in pair bond maintenance. Males and female prairie voles were allowed to cohabitate in a cage for one week. Following the one-week of cohabitation, pairs were given a 2-bottle choice paradigm in cages that contained a mesh divider. Male subjects were then test for their pair bond strength. The results showed that when there was a discrepancy in alcohol consumption between partners, that males display a weaker pair bond compared to when alcohol consumption was matched between partners. These results showed that partner drinking status can influence the maintenance of pair bonds and will potentially lead to alternatives to the current treatments for alcohol use disorder.

Disclosures: **A.T. Walcott:** None. **A. Ryabinin:** None.

Poster

076. Alcohol-Related Behavior

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Support: Department of Psychology, BGSU

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Title: The relative reward effect: Instrumental and consummatory contrast for sucrose in Sprague-Dawley and alcohol-preferring (P) rats

Authors: *J. J. MCGRAW, R. S. GOLDSMITH, K. A. SMITH, M. FILIPOVIC, M. C. MILLER, H. C. CROMWELL
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Abstract: Relative reward effects highlight the impact of reward value shifts on goal-directed behavior. A popular method used to examine relative reward effects is incentive contrast. Positive contrast is an upshift or increase in behavior toward a particular outcome due to an alternative comparison, while negative contrast is the opposite. The ability to compare rewards and utilize value shifts to make advantageous outcome decisions may be disrupted in substance use disorders such as alcohol abuse and addiction. We examined the reward comparison abilities of Sprague-Dawley (SD) and alcohol-preferring (P) rats in an operant task using 12 sucrose solution pairings to determine 1) the impact of food restriction on incentive contrast; 2) potential line differences in incentive contrast before P rat alcohol exposure; 3) the impact of alcohol on incentive contrast in P rats; and 4) the impact of reward value shifts on alcohol intake in P rats. We also sought to determine the relationship between instrumental and consummatory behaviors and the capacity to which these behaviors predict incentive contrast for sucrose solutions. Animals underwent a repeated-measures design consisting of two single outcome blocks (Blocks 1 & 3) separated by a mixed outcome block (Block 2). Appetitive and consummatory measures were used to assess positive and negative contrast toward single outcomes relative to alternatives presented during mixed blocks. Preliminary data on latency to leverpress after nosepoke between Blocks 1 and 2 suggest positive contrast effects for higher sucrose solutions and increased, generalized responding for mixed outcomes in food-restricted SD rats. Nonrestricted SD rats showed reversed contrast effects across all sessions. Between Blocks 1 and 3, restricted SD rats showed positive and negative contrast for 10% sucrose due to its comparison with 5% and 20%

during Block 2, respectively. Nonrestricted SD rats continued to show reversed contrast effects with one negative contrast effect for 5% sucrose due to its comparison with 10% during Block 2. Preliminary results suggest food-restricted SD rats respond faster to higher sucrose outcomes and slower to lower sucrose outcomes while nonrestricted SD rats show the opposite with some ability to respond slower to lower outcomes. Restricted SD rats also show some ability to respond quicker to lower outcomes previously paired with higher outcomes during mixed blocks. Future work will continue to explore the impact of food availability on contrast and examine relative reward effects in alcohol-preferring rats.

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Poster

077. Neural Effects of Ethanol Use

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AA010761

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AA020929

VA Medical Research

Title: Repeated cycles of chronic intermittent ethanol exposure alters neuronal activation in the ventral hippocampus and nucleus accumbens

Authors: *W. C. GRIFFIN, III[1], H. L. HAUN[1], A. K. OLSEN[2], R. L. SMITH[3], R. I. ANDERSON[1], H. A. BOGER[1], H. C. BECKER[1]
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Abstract: Glutamatergic transmission in the nucleus accumbens (NAc) regulates ethanol drinking and an important source of glutamate in the NAc are projection neurons from the subiculum of the ventral hippocampus (vHC). Increasing pathway activity using excitatory DREADDs increases drinking, underscoring the connectivity between these two regions in regulating drinking behavior, and also augments KCl-evoked glutamate release. Additionally, recent retrograde tracing (Ct-B) studies in our laboratory demonstrate projections from the vHC

to the NAc where we previously found increased extracellular glutamate in ethanol dependent mice and that microinjections of glutamatergic agonists/antagonists influence drinking. Using our model of ethanol dependence, the current study evaluated neuronal activation in the vHC and the NAc Shell (NAcS) using cFos as a marker. Male C57BL/6J mice were trained to drink ethanol (15% v/v) in a 2-bottle choice, limited access paradigm. After establishing stable ethanol intake, mice received 4 weekly cycles of chronic intermittent ethanol vapor (16h/d for 4d) (EtOH-DRK group) or air (CTL-DRK group) exposure in inhalation chambers, with each exposure cycle alternating with a week of limited access drinking. Two other groups of mice were similarly handled but not given access to ethanol for drinking (EtOH, CTL groups). Mice were sacrificed for brain tissue collection following the last vapor exposure at 0, 8, 24, 72h and 7d later without drinking. cFos expression was evaluated using standard IHC procedures. At 0h, ethanol exposure by drinking and/or vapor exposure reduced cFos expression relative to CTL mice, though vapor produced the most robust reduction. As expected, acute ethanol withdrawal increased cFos expression (peak at 8h) in the EtOH and EtOH-DRK mice, though the magnitude of the increase in vHC was smaller compared to NAcS. Given our previous findings it was surprising at later time points (72h & 7d) with or without a history of drinking there was a ~50% reduction in cFos expression in both regions, compared to CTL and CTL-DRK mice. Although opposite expectations, the persistent reduction in cFos expression at times when mice would ordinarily resume drinking suggests adaptations in the vHC-NAc pathway may contribute to increased drinking in ethanol dependence. Previous work indicates that post-CIE access to ethanol influences glutamate and future studies will examine whether this also influences neuronal activation.

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Poster

077. Neural Effects of Ethanol Use

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VA Medical Research

Title: Modulation of the anterior paraventricular thalamus influences ethanol consumption and the acquisition of conditioned taste aversion in C57BL/6J mice

Authors: *H. HAUN[1], H. C. BECKER[1,2], W. C. GRIFFIN, III[1]
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Abstract: The paraventricular thalamus (PVT) serves as a key interface for sensory information and higher order processes involved in drug seeking. The PVT sends dense glutamatergic projections to the nucleus accumbens (NAc) shell, which has been implicated in cue-induced reinstatement of drug seeking as well as aversion and reward omission. However, the role of this structure and pathway are not clearly defined in the regulation of alcohol (ethanol; EtOH) consumption. Using a chemogenetic approach, we examined the role of the anterior PVT and aPVT-NAc circuit in binge-like EtOH drinking using the drinking-in-the-dark (DID) model. Glutamatergic projections from the PVT were targeted using an excitatory or inhibitory DREADD under the CaMKII promoter and bilateral guide cannula were implanted above the NAc in adult male C57BL/6J mice. During a binge drinking session (4-hr, 20% EtOH), aPVT excitation with systemic (IP) administration of clozapine-*N*-oxide (CNO, 3mg/kg) compared to vehicle (0.9% saline) decreased EtOH intake at both 2-hr (Veh= 2.01, CNO= 1.2 g/kg) and 4-hr (Veh= 3.74, CNO= 2.95 g/kg) time points (all ps< 0.05). Inhibition of the aPVT had no effect on intake. During the following test, we targeted aPVT-NAc projections by infusing either vehicle or CNO (3μM) into the NAc. Excitation of the aPVT-NAc circuit decreased EtOH intake at both the 2-hr (Veh= 1.94, CNO= 0.97g/kg) and 4-hr (Veh= 3.72, CNO= 1.06 g/kg) time points (all ps< 0.05). Inhibition of the aPVT-NAc circuit did not alter intake. To determine if this decrease in intake after aPVT excitation is related to aversion, a conditioned taste aversion (CTA) test was conducted where mice were given access to 0.1% saccharin for 30-min immediately followed by injection (IP) of vehicle or CNO. Saccharin intake the following day was not affected suggesting that aPVT excitation or inhibition does not have aversive qualities. EtOH-induced CTA was then conducted to determine if the aPVT is involved in initial aversion learning. Mice were given access to 7.2% Kool Aid for 30-min followed by IP injection of EtOH (2g/kg) and either vehicle or CNO. As expected, EtOH combined with vehicle reduced Kool Aid intake by 49% across 4 days. Surprisingly, aPVT inhibition at the time of EtOH administration potentiated aversion by reducing fluid intake 79% across 4 days (all ps<0.05). However, aPVT excitation had no effect on EtOH-induced CTA. These data suggest that aPVT activity is important for maintaining ethanol consumption and may mitigate the aversive qualities of EtOH. Future studies will explore the role of the aPVT in the balance of reward and aversion in dependent mice within the chronic intermittent EtOH (CIE) exposure model.

Disclosures: **H. Haun:** None. **H.C. Becker:** None. **W.C. Griffin:** None.

Poster

077. Neural Effects of Ethanol Use

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Title: Pituitary adenylate cyclase-activating polypeptide in the thalamic paraventricular nucleus: Characterization and response to ethanol intake

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Abstract: The paraventricular nucleus of the thalamus (PVT) is a limbic brain region involved in a number of ingestive behaviors, including ethanol drinking. While this region is known to be dense in neuropeptides, few of them have so far been characterized. Pituitary adenylate cyclase-activating polypeptide (PACAP) has been shown to be expressed in select limbic brain structures and, through genetic knockout, to affect ethanol intake. This neuropeptide is expressed in two isoforms, PACAP-27 and PACAP-38, with PACAP-38 believed to be more heavily expressed in the brain. The purpose of this study was to (1) determine if PACAP is expressed in the PVT, (2) characterize the expression of the PACAP isoforms throughout PVT, and finally (3) determine if PACAP in the PVT is affected by ethanol drinking. Adult male and female Sprague-Dawley rats (n = 5-6/group) were examined using quantitative PCR and fluorescent immunohistochemistry to analyze the gene expression and peptide levels of PACAP in the subregions of the PVT. Adult male Long-Evans rats (n = 6-8/group) were trained to drink 20% ethanol using an intermittent access model, or maintained on water and chow only, and were examined using the same techniques to determine the response of PACAP to ethanol. Our results indicate that PACAP mRNA expression and total number of PACAP-containing cells are high in the PVT, with more PACAP detected in the posterior compared to the anterior subregion of the PVT (42% vs. 52% of all cells in each PVT subregion), but more PACAP in the anterior PVT of female compared to male rats. Furthermore, while PACAP-38 is more densely expressed than PACAP-27, the former is primarily located in fibers while the latter is in PVT cell bodies. Notably, PACAP-38, when found in cell bodies, is always co-localized with PACAP-27. Finally, ethanol drinking leads to a trending increase in PACAP mRNA and number of cells, particularly in the posterior subregion of the PVT, where PACAP expression is endogenously higher. Taken together, these data indicate that elevated PACAP expression in the posterior PVT may play an important role in

alcohol addiction, and may more broadly affect the complex processes that make up ingestive behavior.

Disclosures: A.T. Gargiulo: None. **A. Gupta:** None. **G.R. Curtis:** None. **P. Badve:** None. **S. Pandey:** None. **J.R. Barson:** None.

Poster

077. Neural Effects of Ethanol Use

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Title: Effects of chronic binge-like alcohol drinking on Pde4 gene expression in the nucleus accumbens

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Abstract: Introduction: Recent studies provide strong evidence regarding a potential role for phosphodiesterase (PDE) inhibitors in the regulation of alcohol drinking in mice, rats, and humans. Phosphodiesterase 4 (PDE4) degrades intracellular cyclic adenosine monophospate (cAMP). PDE4 inhibitors increase cAMP signaling and striatal activity. Existing PDE inhibitors target multiple isoforms (*Pde4 a,b,c, or d*; although with varying affinities), and produce different physiological responses. It is not clear which isoform(s) is important for alcohol intake.

Further, it is unknown how alcohol intake affects *Pde4* gene expression. PDE4A and PDE4B are expressed in the ventral striatum [nucleus accumbens (NAc)], a region important in Alcohol Use Disorders. Here, we examine the effects of chronic binge-like drinking on diurnal *Pde4a* and *Pde4b* gene expression in the NAc of mice selectively bred to achieve high blood alcohol levels after a short binge-drinking session (High Drinking in the Dark, HDID-1 mice).
Methods: Adult HDID-1 female mice were provided 8 weeks of limited access 20% ethanol drinking (or water) for 4 days/week. 21 hr after the last limited access session, mice were euthanized at 8 time points over a 24 hr period to determine whether *Pde4* expression 1) exhibits day/night rhythmicity and/or 2) is altered by chronic binge-like drinking. NAc tissue was processed for multiplex qRT-PCR (n=6 mice/treatment/time point; genes of interest= *Pde4a*, *Pde4b*, housekeeping gene=*18s*). Data were analyzed using the ddCT relative gene expression method and two-way ANOVA.
Results: Chronic binge-like drinking significantly increased *Pde4b* expression in the NAc [$F(1,77)=15.4$, $p<0.001$]. Analysis revealed non-significant trends for main effect of time [$F(7,77)=2.07$, $p=0.06$] and group x time interaction [$F(7,77)=1.9$, $p=0.08$]. The effects of chronic binge-like drinking on *Pde4a* were also trends [main effect of group $F(1,77)=3.2$, $p=0.07$]. However, *Pde4a* expression in the NAc varied significantly with time [main effect of time, $F(7,77)=2.3$, $p<0.05$] and for a group x time interaction [$F(7,77)=2.1$, $p=0.05$].
Summary: These experiments demonstrate that chronic binge-like alcohol drinking significantly increases *Pde4b* expression in the NAc. Furthermore, we find that *Pde4* expression in the NAc tends to be rhythmic. Together, these data suggest that targeted inhibition of PDE4B (specifically in the NAc) could reduce high-intensity binge-like drinking.

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Poster

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Title: Interactions between ethanol and stress exposure on long-lasting negative affect-like behaviors and alterations in nucleus accumbens dopamine dynamics

Authors: *K. M. HOLLERAN, A. N. KARKHANIS, S. E. ALBERTSON, S. R. JONES
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Abstract: Comorbidity between alcohol use disorders (AUDs) and disorders of negative affect - such as major depression, generalized anxiety, and post-traumatic stress (PTSD) disorders - is exceedingly high, and individuals who suffer from these conditions in tandem have greater symptom severity and poorer treatment outcomes. Hypodopaminergia is a putative shared component of these disorders, and is thought to underlie in part the anhedonia common to these conditions. The occurrence of both AUDs and disorders of negative affect is heightened following stressful experiences. We used two preclinical models of stress exposure, repeated forced swim stress (FSS) and mouse single prolonged stress (mSPS), in C57Bl/6J mice either alone or in conjunction with alcohol dependence induced via chronic intermittent ethanol (CIE) exposure to vaporized ethanol (EtOH). We found that CIE exposure alone drives negative affect-like behaviors both early (72hrs) and late (2 weeks) into withdrawal via the marble burying task and novelty-suppressed feeding task, respectively. Exposure to the mSPS paradigm, a relatively recent model of PTSD, increased anxiety-like behavior, augmenting thigmotaxis in a novel open field arena. When FSS was interleaved between cycles of CIE, negative affect-like behavior and dependence-induced escalation of EtOH consumption was greater than with exposure to either CIE or FSS alone. Finally, we examined dopamine (DA) dynamics in the nucleus accumbens using fast scan cyclic voltammetry (FSCV) after exposure to CIE, FSS or mSPS, or a combination thereof. We found that CIE produces hypodopaminergia as measured by reduced stimulated DA release as long as 4 weeks after withdrawal and faster reuptake early in withdrawal (0-72hrs). Stress exposure alone resulted in increased stimulated release and faster reuptake, lasting at least 3 weeks following the stressor. Finally, both stress and CIE exposure augmented the dopamine inhibiting effect of kappa opioid receptor (KOR) stimulation by the agonist U50,488. Taken together, these data indicate that EtOH and stress exposure, alone or in combination, exert powerful long-lasting alterations to affective states that may be driven in part through neural adaptations of the nucleus accumbens dopamine system.

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Poster

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Title: EtOH-evoked enhancement of the H-current significantly amplifies DA neuron responses to synaptic inputs

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Abstract: Alcohol addiction has been hypothesized to result from persistent neuroadaptations in the brain. However, the mechanisms of this neuroadaptations, and the influence of EtOH in general, are not precisely known. Reinforcing properties of ethanol are thought to be mediated by its ability to increase midbrain dopamine (DA) neuron firing acting through multiple intrinsic and synaptic targets. Among intrinsic currents, the most prominent effect is the enhancement of a hyperpolarization-activated cation current (Ih). However, potentiation of Ih in *in vitro* conditions produces only a minor effect on the firing frequency of the DA neuron, making it unclear how it can promote high frequency burst firing. Based on a biophysical model of VTA microcircuitry, we found that: (1) intrinsic changes in the DA neuron under EtOH boost its response to synaptic currents and amplifies burst firing. These bursts are mostly elicited through NMDA receptor currents, and these responses are potentiated by EtOH via interaction of NMDA and Ih. Critically, we found that, by enhancing the Ih current, EtOH switches the DA neuron excitability from type I to type II and, consequently, induces higher DA transients through increases synchronization among DA neurons; (2) potentiation of the Ih current increases DA neuron sensitivity to synchronous GABAR inputs. Previously, we have shown that pulsatile synchronous GABA inputs are capable of increasing DA neurons firing and bursting. The interaction of Ih and GABA currents leads a significant DA frequency increase that can be achieved for wide range of input parameters. Further, enhanced Ih can cause complex burst DA neuron firing patterns in the absence of bursting inputs.These simulations suggest that DA neurons process synaptic inputs differently under EtOH. Even though enhancement of Ih produces only a minor effect on DA cell pacemaking, it can lead to a several-fold elevation of DA firing frequency under synaptic inputs. We suggest above as a mechanism reconciling moderate DA firing rate increase by ETOH in vitro and , strong in vivo frequency modulation, burst activity induction, and increase of DA concentrations in the projection areas.

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Poster

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Title: Ethanol, calcium and growth cone dynamics in immature GABAergic cortical interneurons

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Abstract: Prenatal exposure to ethanol disrupts the normal pattern of tangential migration of cortex-bound primordial GABAergic interneurons, and this has been postulated to contribute to the etiology of fetal alcohol spectrum disorder (FASD). There is evidence that ethanol interacts with $GABA_A$ receptors that are tonically activated by ambient GABA to exert this effect but, beyond this, the cellular and subcellular mechanisms are largely unexplored. Here we initiated a pilot project to establish the experimental premise for investigating the mechanisms linking ethanol, $GABA_A$ receptor activation and aberrant migration.

First, we asked whether ethanol exposure affected the migration of GABAergic interneurons. Dissociated primary cultures were prepared from E14.5 Nkx2.1Cre/tdTomato embryos and maintained without or with 0.67mM ethanol (30mg/dl or 0.03% equivalent), and individual tdTomato-fluorescent cells were imaged 18-24 hours after plating. In fixed cultures, immunostaining of actin and α-tubulin revealed that ethanol exposure decreased the mean area/size of lamellipodia and the number of filopodia, consistent with enhanced migratory activity. Real-time videomicroscopy indicated that this is associated with altered patterns of protrusion and retraction of filopodia.

Second, since calcium is implicated in regulating neuronal migration and cytoskeletal dynamics, we asked whether ethanol may affect growth cone dynamics by regulating intracellular calcium via calcium channels. To this end, organotypic slice cultures were prepared from sex-genotyped male and female E14.5 Nkx2.1Cre/tdTomato embryos and assigned to four groups: Control, 20μM Nifedipine, 20μM Nifedipine+0.67mM Ethanol and 0.67mM Ethanol. The slice cultures were maintained for 27 hours, fixed and tdTomato-fluorescent cells were counted to provide an index for the extent of tangential migration. Preliminary results indicate that the addition of the calcium channel blocker nifedipine prevented the ethanol-induced aberrant tangential migration. In dissociated cultures, embryonic GABAergic interneurons were immunopositive for $CaV_{1.2}$. Ongoing experiments are employing the ratiometric calcium indicator fura-2 to monitor ethanol-induced changes in intracellular calcium and correlate this with changes in growth cone dynamics.

Our results are consistent with ethanol affecting tangential migration by changing the calcium dynamics in immature GABAergic cortical interneurons. The present study sets the stage for filling mechanistic gaps that link ethanol exposure with downstream subcellular mechanisms that lead to altered intracellular calcium and growth cone dynamics.

Disclosures: S.M. Lee: None. **F.L. Anderson:** None. **P.W.L. Yeh:** None. **H.H. Yeh:** None.

Poster

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Title: Uncovering the roles of ion channel activity and cytoskeletal remodeling using RNA-seq in rat hippocampus following adolescent ethanol exposure

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Abstract: INTRODUCTION: Excessive alcohol use is common among adolescents and young adults and has been associated with an increased risk of developing an alcohol use disorder later in life. In order to uncover novel targets that may be involved in the long-term effects of adolescent intermittent ethanol exposure we conducted RNA-seq to understand the temporal changes in hippocampal gene expression in the rat.
METHODS: Beginning at PND30 (adolescence), Sprague Dawley rats received chronic intermittent ethanol (5g/kg i.g. 10 times across 16 days). Rats were euthanized and hippocampal tissue was collected at 24hr after the 4th dose, 24hr after the last dose, and 24 days after the last dose. RNA-seq was performed using TrimGalore toolkit and gene counts were compiled using the HTSeq tool. False discovery rate was calculated to control for multiple hypothesis testing and gene set enrichment analysis was performed to identify differentially regulated pathways.
RESULTS: At the earliest time-point (24hr after the 4th dose), following repeated ethanol exposure, there was gene enrichment of negative regulators of cellular component organization and genes associated with metallopeptidases and mitochondrial function. At the second time-point (24hr after the last dose), ethanol exposed rats showed gene enrichment for glutamate and voltage gated potassium activity-related pathways, neuron differentiation, synaptic transmission, and synaptic organization. Interestingly, a number of immune response genes were downregulated at this time-point. At the adult time-point (24 days after the last dose), ethanol exposed rats showed highly enriched gene sets involved in cytoskeletal remodeling.
CONCLUSION: These data provide detailed insight into how hippocampal gene expression changes across adolescence and into adulthood. Our findings also provide a comprehensive screening of the acute and long-term effects of adolescent ethanol exposure on gene expression. Some of the findings presented here support our previous work demonstrating long-term upregulation of proteins that are involved neuronal remodeling. These data also uncover novel

pathways that will be an invaluable guide into understanding the mechanisms underlying the acute and long-term effects of adolescent ethanol exposure.

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Poster

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ARC FT1110884 to SEB

Title: Chronic binge-like alcohol consumption alters the excitatory/inhibitory balance of 5-HT neuron connectivity in the mouse brain

Authors: *A. BELMER, S. E. BARTLETT
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Abstract: Serotonin (5-HT) is a neuromodulator of both excitatory (Glutamate) and inhibitory (GABA) synaptic transmission in the brain. Since chronic alcohol exposure was shown to alter both serotonin, glutamate and GABA signalling, we used our recently published quantitative approach combining high resolution microscopy and 3D reconstruction of 5-HT neuron connectivity to determine the consequences of prolonged (12 weeks) alcohol binge-like consumption in the Drinking-in-the-Dark (DID) on 5-HT axons connectivity onto excitatory and inhibitory synapses throughout the mouse brain, including the prefrontal cortex (PFC), the nucleus accumbens(NAC), the bed nucleus of the stria terminalis (BNST), the amygdala, the hippocampus (HIP) and the ventral tegmental area (VTA). Our results show that long-term chronic alcohol binge consumption produces profound maladaptive reorganizations of the excitatory/inhibitory balance of 5-HT neuron connectivity in particular brain regions involved in the control of anxiety and depression-related behaviours, which could explain some of the emotional and mood-related deficits associated with alcoholism.

Disclosures: A. Belmer: None. **S.E. Bartlett:** None.

Poster

077. Neural Effects of Ethanol Use

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Title: Alpha 6-containing nicotinic acetylcholine receptor is a sensitive target for low-dose alcohol

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Abstract: Unlike other addictive drugs (e.g., morphine, cocaine or nicotine) that have specific molecular targets, there is no clear consensus regarding a target for ethanol. In most studies, EtOH concentrations used were too high (e.g., >50 mM) compared to the EtOH concentrations in human brain associated with alcohol drinking and reward, and high-dose EtOH likely produces non-specific modulations of a variety of receptors, ion channels, intracellular signaling cascades, and gene expression in the brain. Thus, it is important to understand the molecular mechanism of the low-dose (e.g., <10 mM) rewarding effects of EtOH. nAChRs containing α6 subunits (α6*-nAChRs) evinced a highly restricted distribution in midbrain dopaminergic neurons that are associated with drug dependence and addiction. The fundamental goal of this study was to examine the effects of low-dose EtOH on α6*-nAChR heterologously expressed in human SH-EP1 cells using patch-clamp whole-cell recordings. Co-transfection of human nAChR α6(N-terminal)/α3(transmembrane domain) chimera and β2, β3 subunits into human SH-EP1 cells formed a functional a6-containing nAChR (α6*-nAChR). Patch-clamp whole-cell recording demonstrated that the transfected α6*-nAChR is highly sensitive to the α6 subunit selective antagonist, α-conotoxin MII (to 1 μM NIC, MII IC_{50}= 10.3±1.2 nM, Hill coefficients=0.9±0.1, n=10). Nicotine (NIC) concentration-response relationship curve showed NIC EC_{50} values and Hill coefficients are 0.34±0.02 μM and 0.7±0.1 (n=10). We evaluated the effects of different concentrations of EtOH (from 0.01 to 50 mM) on 1 μM NIC-induced currents, and found that EtOH modulates NIC currents in an EtOH concentration-dependent manner. Low, but not high,

doses of EtOH enhance NIC currents, forming a bell-shaped EtOH concentration-efficient curve with a maximal potentiation effect (about 125%) between EtOH 0.1 and 0.5 mM. We then evaluated the effects of 0.5 mM EtOH on different concentrations of NIC (from 1 nM to 30 μM), and found that EtOH potentiates NIC response in a NIC concentration-dependent manner, the enhanced effect declining with an increase in NIC concentrations, with a maximal potentiation at 10 nM NIC. In conclusion, our results demonstrate functional α6*-nAChRs transfected in human SH-EP1 cells that can be used as an excellent cell model to investigate α6*-nAChR function and pharmacology. Under patch-clamp recording conditions, low-dose EtOH affects α6*-nAChR function as a positive allosteric modulator.

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Poster

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Title: Alcohol consumption alters calcium signal dynamics in the medial prefrontal cortex

Authors: *J. A. RINKER[1], W. C. GRIFFN, 3rd[2], L. PASSARELLA[3], P. J. MUHOLLAND[1]
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Abstract: Alcohol dependence is a chronic relapsing brain disorder characterized by uncontrollable, heavy alcohol consumption. Chronic, heavy alcohol exposure is known to alter activity in a number of brain regions,including the medial prefrontal cortex (mPFC). The mPFC is heavily involved in value-based decision making, and alcohol has been shown to alter the plasticity and excitability of mPFC pyramidal neurons. Gradual changes in the hyperexcitability of mPFC neurons may contribute to the loss of control over alcohol consumption characteristic of dependence. Understanding the dynamics of signaling in the mPFC during consumption of alcohol prior to, and ultimately after the development of, dependence is important for defining how mPFC activity contributes to heavy alcohol consumption. Here we used fiber photometry to record calcium signaling in the mPFC using the genetically encoded calcium indicator,

GCaMP6s. Either *Thy1*-GCaMP6s transgenic mice which express GCaMP6s primarily in deep-layer cortical pyramidal neurons or C57BL/6J mice with AAV1-hSyn-GCaMP6s-WPRE virus mediated GCaMP6s expression in all neurons in the mPFC were used in these studies. Mice were implanted with a 400 µm multimodal fiber optic implant into the prelimbic mPFC. GCaMP6s signal integrity was tested by briefly anesthetizing mice with isoflurane or by a brief startle. We then recorded calcium transients in freely moving mice during access to water, sucrose, or alcohol in homecages equipped with lickometers to timestamp consummatory behavior with the fluorescent signal. As expected, isoflurane inhalation produced a dramatic drop in the calcium signal that returned to baseline during recovery from anesthesia. In contrast, analysis revealed a potentiation of the signal immediately following the startle. Interestingly, there was a significant reduction in the calcium signal at the onset of licking for all three solutions that rebounded back to pre-consumption levels at the termination of the bout. This phenomenon was much more robust and reliable for sucrose and alcohol in comparison with water. This effect was not a result of lack of movement during the drinking bout, as the calcium signal did not decrease during periods of no movement not associated with consumption. Additionally, this robust drop in calcium signal at initiation of consumption was more defined in *Thy1*- GCaMP6s transgenic mice compared to C57BL/6J mice infected with GCaMP6s in all neurons, presumably due to cell-type specific expression. Overall, these results show a complex shift in calcium signal dynamics during bouts of licking for rewarding solutions and provide insight into the role of mPFC in consummatory behaviors.

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Poster

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R25 GM076162

Title: Brain corticosterone levels are altered in amygdala following chronic intermittent ethanol exposure and withdrawal in C57BL/6J mice

Authors: *A. M. HILL[1], A. KAMPOV-POLEVOI[2], A. MORROW[3], A. M. MALDONADO-DEVINCCI[4]
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Abstract: Chronic ethanol exposure produces dependence in rodents, primates and humans. Ethanol dependence is marked by increased anxiety, seizure susceptibility, and impaired cognition. Exposure to stressors can have similar effects and induce changes in brain responses to ethanol. Recently, we showed that chronic intermittent ethanol (CIE) exposure and withdrawal altered levels of the most potent and abundant GABAergic neuroactive steroid, (3α,5α)-3-hydroxy-pregnan-20-one (3α,5α-THP) in various limbic brain regions of mice. We propose that CIE exposure and withdrawal induces a change in neuroactive steroid biosynthesis. Recent work showed that brain corticosterone levels were increased in the hippocampus and cortex following acute administration of ethanol. Therefore, in the present work, we determined if a compensatory increase in brain corticosterone levels would be observed in the amygdala and hippocampus, areas where changes in brain 3α,5α-THP levels were seen following CIE exposure and withdrawal. Male C57BL/6J mice were exposed to ethanol vapor or untreated air intermittently over the course of four weeks (16 hours/day for 4 days/week). Eight or 72 hours following the final exposure cycle, the mice were euthanized, the brains were perfused, fixed with paraformaldehyde, and collected for analysis of local brain corticosterone immunoreactivity. In the lateral amygdala, CIE exposure and withdrawal reduced brain corticosterone immunoreactivity following 8 hr withdrawal (-25.5±11.4%, p=0.02). However, brain corticosterone levels returned to baseline levels following 72 hr withdrawal. In the central nucleus of the amygdala, brain corticosterone levels were unchanged following 8 hr withdrawal and were increased by 223.4±66.6% (p=0.01) following 72 hr withdrawal. In the CA1 pyramidal cell layer of the hippocampus, brain corticosterone levels were not altered at either withdrawal time point. We are currently investigating changes in corticosterone levels in other brain regions that mediate anxiety, stress, and reinforcement involved in ethanol dependence. Together, these data may provide new insight into brain regions vulnerable to ethanol-induced changes in neuroactive steroids that are important for the development of alcohol use disorders.

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Poster

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Title: Acute dopamine depletion alters functional connectivity of the vta and prefrontal cortex in male social drinkers

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Abstract: Attentional bias (AB) to addiction-related stimuli is thought to reflect Pavlovian-conditioning processes. AB to alcohol cues has been reported in those with an alcohol use disorder (AUD) and in heavy social drinkers. fMRI data suggest that mesocortical connections between the prefrontal cortex (PFC) and the ventral tegmental area (VTA) encode reward-predictive cues. To test the relationship between AB to alcohol cues, mesocortical connectivity, and dopamine (DA) signaling, we acutely depleted DA by administering a DA precursor deficient amino acid beverage, using a double-blind, placebo-controlled, within-subject design. We compared functional connectivity between PFC subregions and the VTA during resting state fMRI in the control and depleted beverage conditions. In addition, we measured AB to alcohol cues in spatial cueing and attentional blink tasks under both conditions. Our sample included 24 male alcohol users (ages 22-40), n=13 light drinkers (LD) and n=11 heavy, binge drinkers (HBD). Using a priori probabilistic atlas-based regions of interest (ROI), we measured ROI to ROI connectivity between the VTA and PFC ROI. We did not observe any main effects of group on mesocortical connectivity. We did find a main effect of beverage on functional connectivity between the VTA and the right superior frontal gyrus (rSFG; $F_{(1, 22)}$= 5.49, p=.029), such that DA depletion increased functional connectivity between the VTA and rSFG. We also detected trends toward significant interactions between drinking group and beverage in two VTA-PFC connections. First, VTA-rSFG connectivity increased in the depleted condition substantially more in the HBD group (r= -.085 vs. .102) relative to the LD group (r= .001 vs. .019; $F_{(1,22)}$=3.70, p=.067). Second, DA depletion decreased functional connectivity between the VTA and left Inferior Frontal Gyrus (lIFG; r= -.018 vs. -.067), whereas the same depletion increased connectivity between the VTA and the lIFG in the LD group (r= -.127 vs. .017; $F_{(1, 22)}$= 3.77, p=.065). Finally, the change in AB to alcohol cues in the spatial cuing task following DA depletion positively correlated with the change in functional connectivity with the VTA and right orbitofrontal cortex (rOFC; r= .417, p=.043), suggesting that connections between the VTA and OFC may enable the capture of attention by alcohol cues. These results suggest that phasic DA release, and its modulation of mesocortical circuitry, plays a complex and subtle role in AB.

Disclosures: **M. Faulkner:** None. **A. Paulson:** None. **L. Harvey:** None. **D.L. Robinson:** None. **C.A. Boettiger:** None.

Poster

077. Neural Effects of Ethanol Use

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 077.14/NN27

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIGMS COBRE: The Delaware Center for Neuroscience Research Grant 1P20GM103653 - 01A1

University of Delaware Office of Graduate and Professional Education Winter Fellowship

Title: Persisting damage to thalamic nucleus reuniens following PD4-9 alcohol exposure suggests alterations to prefrontal-thalamo-hippocampal circuitry in rodent model of fetal alcohol spectrum disorders

Authors: *Z. GURSKY, A. Y. KLINTSOVA
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Abstract: Human alcohol exposure (AE) *in utero* can result in a host of developmental abnormalities, including impaired executive function (EF) (Khoury et al., 2015). In animal models, AE during the brain growth spurt (third trimester in humans; first 2 postnatal weeks in rats) targets structures, undergoing differentiation, layer formation and synaptogenesis, including hippocampus (HPC) and prefrontal cortex (PFC) (Ikonomidou et al., 2000). HPC-PFC interactions are essential for behaviors constituent of EF (Hallock et al., 2016), and are mediated by thalamic nucleus reuniens (RE) (Ito et al., 2015). AE during the brain growth spurt results in altered place learning (Murawski et al., 2012) which is strongly influenced by RE activity (Xu & Südhof, 2013), thus we hypothesized that rats exposed to ethanol on postnatal days (PD) 4-9 will display persistent RE damage, while neighboring thalamic nuclei would be unaffected.
Between PD4 and 9, rat pups underwent one of three treatments: binge exposure to ethanol via intragastric intubation (AE; 5.25 g/kg/day), sham intubation without ethanol (SI), or left undisturbed (SC). Adult female rats were perfused first with 0.1M PBS then with 4% paraformaldehyde in 0.1M PBS on PD72, brains were removed, and coronal serial sections were stained with cresyl violet. The optical fractionator technique was utilized to obtain an unbiased stereological estimate of cell number and volume of three thalamic nuclei: RE, rhomboid (RH), and mediodorsal (MD).
Since SI females did not differ from SC females on any measures (p's>.10), all subsequent analyses were performed between SI and AE groups. AE animals display cell loss and volume

loss in RE ($F_{1,8}$=33.89, p<.01 and $F_{1,8}$=6.00, p=.04, respectively), but do not demonstrate differences in cell number or volume in RH ($F_{1,8}$=1.96, p=.20; $F_{1,8}$=1.49, p=.26) or MD ($F_{1,8}$=3.03, p=.12; $F_{1,8}$=4.44, p=.07). RE cell loss remains significant when changes in RE volume are statistically controlled for ($F_{1,7}$=23.59, p<.01). These data suggest that AE during the brain growth spurt in rat produces permanent and specific reduction in thalamic RE cell number and size, as no effect is observed in other regions of thalamus that are differentially integrated in PFC-HPC circuitry. Further analysis of this tissue will assess whether cell loss specifically targets neuronal or non-neuronal populations in RE. Permanent loss of neurons in RE could produce a shortage in connectivity in HPC-RE-PFC circuitry and underlie abnormalities in behaviors that rely on the integrity of this circuitry.
Supported by NIH/NIGMS COBRE: The Delaware Center for Neuroscience Research Grant 1P20GM103653 - 01A1 to AYK and UD OGPE Winter Fellowship to ZHG.

Disclosures: Z. Gursky: None. **A.Y. Klintsova:** None.

Poster

077. Neural Effects of Ethanol Use

Location: Halls A-C

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Program#/Poster#: 077.15/NN28

Topic: G.08. Drugs of Abuse and Addiction

Title: Resting state functional connectivity of the amygdala in alcohol consumers

Authors: *S. HU[1], S. ZHANG[2], K. A. FISCHER[1], C.-S. R. LI[2]
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Abstract: The amygdala is most notably associated with the emotion of fear through its functional activation to negative valence and resting state connectivity with cortical regions, especially the medial prefrontal cortex (mPFC). Previous research showed that acute alcohol consumption was associated with increased connectivity between the amygdala and the mPFC, including the anterior cingulate cortex (ACC) when viewing faces with negative emotion. However, the relationship between the amygdala-prefrontal connectivity and alcohol consumption in healthy adults remains unclear. In this study, we used whole-brain analysis to examine the resting state connectivity of the amygdala using probabilistic maps from its subdivisions as a function of alcohol consumption. Resting-state functional magnetic resonance imaging (fMRI) scans were obtained from the Nathan Kline Institute (NKI)/Rockland sample (Nooner et al., 2012). Measures on drinking behavior were obtained from the NIDA Quick Screen V1.01. Eighty-three adult participants (26 females) between the ages of 18 and 89 who showed a valid substance involvement (SI) score of alcohol use were selected for the connectivity analysis. The mask of amygdala was obtained from the SPM Anatomy Toolbox Version 2.2c (Eickhoff et al., 2005; 2006; 2007) created based on the cytoarchitectonic

probabilistic map. Four subdivisions were segregated: the superficial, latero-basal, centro-medial, and amygdalostriatal transion area. For each participant, we extracted the BOLD time course of each subdivision and computed the correlation coefficient between the average time course of each region and that of all other brain voxels. In the group analysis, we correlated the Z map from each subdivision with the alcohol SI score. Results showed that the amygdala is positively connected with the inferior frontal polar areas and basal ganglia, and negatively connected with the medial prefrontal cortex, inferior parietal lobule, and cuneus. In addition, the dorsal ACC in the connectivity map of latero-basal amygdala showed negative correlation with alcohol SI. These results suggested interrupted connectivity in the amygdala-prefrontal circuitry associated with alcohol consumption in healthy adults.

Disclosures: **S. Hu:** None. **S. Zhang:** None. **K.A. Fischer:** None. **C.R. Li:** None.

Poster

077. Neural Effects of Ethanol Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: Bruce Jones Fellowship

R01AA15167

U01AA16651

Title: Ethanol modulation of the synaptic properties of mouse agranular insular cortex pyramidal neurons

Authors: ***J. E. SHILLINGLAW**[1], H. C. RADFORD[2], R. A. MORRISETT[2]
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Abstract: The Insular Cortex (Insula) is an interoceptive region that represents and processes bodily states. Prior human and animal studies suggest a role for the Insula and interoception in the etiology of substance use disorders. The Agranular Insular Cortex (AIC), a subregion of the Insula, has received the majority of addiction interest because multiple levels of research suggest it has roles in both positive and negative drug reinforcement. The AIC has shown relatively high expression levels of dopamine-1 receptors and corticotropin-releasing factor-1 receptors, indicated in positive and negative drug and alcohol-reinforcement, respectively. Additionally, rodent behavior in models of positive and negative drug-reinforcement is sensitive to AIC manipulation. Despite these data indicating a role for the AIC in development and/or maintenance of substance use disorders, to our knowledge no one has investigated whether the

AIC is a direct target for the effects of ethanol. Therefore, we investigated whether acute ethanol modulates the basic synaptic properties of the major fast excitatory and inhibitory neurotransmitter systems in the AIC, glutamate and gamma-aminobutyric acid (GABA), respectively. Whole-cell, voltage clamp configuration was obtained in layer 2/3 pyramidal AIC neurons of adult male C57BL/6J mice, and the effects of ethanol on pharmacologically isolated glutamatergic and GABAergic synaptic transmission were determined. We found that 50mM ethanol did not change the mean amplitude or mean frequency of spontaneous excitatory postsynaptic currents or inhibitory postsynaptic currents. We then investigated whether ethanol modulates evoked glutamatergic transmission, and found that pharmacologically relevant concentrations of ethanol inhibit evoked n-methyl-d-aspartate receptor (NMDAR) currents, but not evoked α-amino-3-hydroxy-5-methylisoxazole-4- propionic acid receptor currents. Taken together, these data indicate that glutamatergic transmission in layer 2/3 pyramidal AIC neurons is sensitive to pharmacologically relevant doses of ethanol. Since this glutamatergic sensitivity to ethanol in the AIC is specific to NMDARs, it suggests NMDAR-mediated glutamatergic processes in the AIC may be particularly disrupted by ethanol.

Disclosures: **J.E. Shillinglaw:** None. **H.C. Radford:** None. **R.A. Morrisett:** None.

Poster

077. Neural Effects of Ethanol Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant MH093650

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Title: Chronic intermittent alcohol drinking recruits the pituitary adenylate cyclase-activating polypeptide (PACAP) system in the bed nucleus stria terminalis (BNST) of mice

Authors: *S. G. QUADIR, A. FERRAGUD, R. M. LEAVITT, V. SABINO, P. COTTONE
Pharmacol. and Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA

Abstract: Alcohol Use Disorders (AUDs) are very serious and complex neuropsychiatric diseases characterized by increased alcohol intake, inability to control consumption and a negative emotional state in absence of alcohol. In addition, repeated cycles of alcohol intoxication and abstinence are known to induce neuroplastic alterations in specific brain regions, alterations which in turn trigger and sustain excessive alcohol drinking. One brain area that has been proposed to play a critical role in AUDs is the bed nucleus of the stria terminalis

(BNST). Specifically, the pituitary adenylate-cyclase activating polypeptide (PACAP) system in the BNST has been proposed to be a master regulator of the stress response. Here we aim to bridge the gap between these areas of research and determine the role of PACAP in the BNST in regulating alcohol drinking. Using a two bottle choice chronic intermittent ethanol paradigm, we observed that female mice drink significantly more alcohol and show higher preference, compared to male mice. Importantly, we found that chronic intermittent alcohol exposure increases PACAP immunoreactivity in the BNST of both male and female mice. These data lay the foundation for more extensive studies which may lead to the identification of a neuropeptide system with a critical role in heavy alcohol drinking. A deeper understanding of the specific neuroadaptations produced by chronic alcohol will be essential for the discovery of novel therapeutic agents to alleviate alcoholism.

Disclosures: S.G. Quadir: None. **A. Ferragud:** None. **R.M. Leavitt:** None. **V. Sabino:** None. **P. Cottone:** None.

Poster

077. Neural Effects of Ethanol Use

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ABMRF

Indiana Alcohol Research Center

Title: Alcohol consumption related decision-making encoding is altered in the prefrontal cortex of alcohol preferring rats

Authors: *N. TIMME[1], D. N. LINSENBARDT[2], C. C. LAPISH[1]
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Abstract: In addition to research on reward systems, recent research has identified alterations in decision-making as critical for the expression of addictive behaviors. Therefore, it is vital to understand the role that altered decision-making plays in addiction. To assess changes in

decision-making related to addiction, we performed *in vivo* electrophysiological recordings in the dorsal medial prefrontal cortex (mPFC, a brain region heavily involved in decision-making) of a validated rodent model of excessive drinking (alcohol preferring (P) rat) and a control rat line (Wistar) during a simple cued alcohol drinking task. During this task, a visual signal was used to cue the animal that alcohol would become available on a certain side of an operant chamber. We used dynamic information theory to examine changes in alcohol cue, alcohol availability, and decision outcome encoding throughout this task by individual neurons and neural population signals. Encoding was assessed using mutual information and neural population signals were obtained via principal component analysis of individual neural spiking data. At the individual neuron level, we found that P rats showed increased encoding of alcohol availability as compared to Wistars. Also, we found that decision outcome encoding was significantly decreased in P rats before the cue, during the cue, and during drinking as compared to Wistars. At the neural population level, we found consistent decreases in decision outcome encoding during drinking in P rats across dominant principle components, as well as decreases in alcohol cue encoding as compared to Wistars. Taken together, these results indicate that encoding of the choice to drink is diminished in the mPFC in animals with a genetic risk for excessive drinking (P rats). Given the importance of the mPFC in decision-making, these results provide evidence that the neural processes underlying decision-making are fundamentally altered in excessive drinking animals.

Disclosures: N. Timme: None. **D.N. Linsenbardt:** None. **C.C. Lapish:** None.

Poster

077. Neural Effects of Ethanol Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: PHS NIH F30 AA025534

PHS NIH R01 AA023410

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Title: The effects of prenatal ethanol exposure on radial migration and the development of pyramidal neurons in the somatosensory cortex

Authors: *L. C. DELATOUR, H. H. YEH
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Abstract: Ethanol is a teratogen that significantly affects normal cortical development. The broad range of brain and behavioral abnormalities associated with prenatal exposure to ethanol

constitute Fetal Alcohol Spectrum Disorder (FASD), a leading cause of preventable intellectual disability. However, the mechanisms leading to the detrimental effects of prenatal ethanol exposure on corticogenesis are not fully understood. We previously reported that prenatal ethanol exposure disrupts tangential migration of GABAergic interneurons during embryonic corticogenesis. This process and the radial migration of glutamatergic pyramidal neurons are intricately interwoven, but the effect of prenatal ethanol exposure on the latter is underexplored. We therefore asked whether prenatal ethanol exposure affects radial migration in the short term, and pyramidal neuron form, function, and their proper integration into the circuitry of the somatosensory cortex in the longer term.

We employed a binge-drinking paradigm in which pregnant mice were exposed to ethanol (5% in liquid food) from embryonic day (E) 13.5 through E16.5, spanning the height of cortical neurogenesis and migration. In the presumptive somatosensory cortex of ethanol-exposed embryos, we noted aberrant distribution of Tbr1 and Cux1 immunofluorescence, indicative of a disruption in radial migration. However, BrdU and Ki67 expression suggests that these changes were not due to altered neuronal proliferation.

Using whole cell patch clamp electrophysiology, pharmacologically isolated spontaneous inhibitory and excitatory postsynaptic currents were recorded in pyramidal neurons in postnatal mice during a period of active synaptogenesis. Our results indicate an increase in both in layer V/VI pyramidal neurons following prenatal ethanol exposure, but not in layer II/III. A Sholl analysis conducted on neurobiotin-filled pyramidal neurons revealed a transient decrease in dendritic complexity in ethanol-exposed postnatal mice. We are currently comparing the optogenetically- and electrically-evoked responses in pyramidal neurons of control and ethanol-exposed postnatal transgenic mice to investigate synaptic properties and the overall circuitry in the somatosensory cortex.

These results suggest that binge-type prenatal ethanol exposure disrupts radial migration and has enduring effects on pyramidal neuron synaptic activity and morphology that is layer specific in the somatosensory cortex. We will continue to investigate the embryonic etiology of FASD by focusing on elucidating the effects of prenatal ethanol exposure on cortical circuitry development in the somatosensory cortex.

Disclosures: L.C. Delatour: None. **H.H. Yeh:** None.

Poster

077. Neural Effects of Ethanol Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA013498

VA Grant BX001271

Title: Alcohol regulates activity of large conductance, Ca^{2+} activated K^+ (BK) single channels in the central nuclei of amygdala in mice

Authors: Q. LI[1], C. CONTET[2], S. N. TREISTMAN[3], *S. D. MOORE[4]
[1]Psychiatry, Duke Univ. Med. Ctr., Durham, NC; [2]Scripps Res. Inst., La Jolla, CA; [3]Inst. of Neurobiology-UPR, MSC, San Juan, PR; [4]Duke Univ., Durham, NC

Abstract: Large conductance Ca^{2+} activated K^+ (BK) channels are present throughout the brain and exert regulatory actions on neurons by affecting membrane potential repolarization, neuronal excitability and neurotransmitter release. The role of BK channels in the central amygdala nucleus in response to acute acute ethanol challenge is not well understood. We performed BK single channel recordings from soma of CeA neurons in male mice in outside-out configuration at 35°C and measured effects of acute of ethanol exposure on somatic BK single channels. Somatic single channels activities were isolated from patches excised from CeA neurons, with patches held at +10 mV or above or under a ramp protocol (-60 to 100mV). The BK channel activity was either sporadic or robust. Bath application of the BK channel blocker paxilline (10 μM) attenuated single channels activities (n=3 patches). Furthermore, these single channels were reversibly blocked by removal of Ca^{2+} (n=3 patches). These results indicate that these currents are voltage-dependent and calcium-dependent BK single channels expressed in CeA neurons. To determine if ethanol affects BK single channel activation, we first bath-applied ethanol (50 mM) and found that ethanol significantly increased the openings of BK channels in a total of 9 somatic patches isolated from CeA neurons in four C57/B6 mice. We further isolated BK channels from BK-β4 KO CeA neurons (n=7 patches/4 mice) and WT CeA (n=7 patched/2mice) and found that ethanol (25 or 50mM) could still potentiate BK single channel activity in the 5 out of 7 somatic patches isolated from BK-β4 KO CeA neurons. Since CeA neurons exhibit distinctive firing patterns, acute effects of BK single channels recorded from CeA neurons with different firing patterns [late firing (n=8), regular (n=10) and single (n=2) from ten C57/B6 mice] were also examined. Ethanol (25 and 50mM) potentiated the BK single channels, and this potentiation appeared to be independent of their firing patterns. Our preliminary results suggest that CeA neurons possess functional BK channels and ethanol exerts a potentiation of these BK single channels in the absence of BK β4-subunits.

Disclosures: Q. Li: None. **C. Contet:** None. **S.N. Treistman:** None. **S.D. Moore:** None.

Poster

077. Neural Effects of Ethanol Use

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NIH R01 AA 016022

Title: D2 dopamine autoreceptor sensitivity is increased in the dorsolateral striatum of C57BL6J mice following chronic ethanol consumption

Authors: *A. G. SALINAS[1,2], Y. MATEO[1], D. M. LOVINGER[1]
[1]Natl. Inst. On Alcohol Abuse and Alcoholism, Rockville, MD; [2]George Mason Univ., Fairfax, VA

Abstract: The development of alcohol use disorders, including alcoholism, involves an increase in habitual behaviors. The dorsolateral striatum (DLS) has been implicated in neurobiological and behavioral processes including learning, drug abuse, and habitual behaviors. Interestingly, a role for dorsolateral D2 dopamine receptors (D2DRs) in mediating habitual behaviors has been shown, although which population of dorsostriatal D2DRs has not been determined (i.e. those on spiny projection neurons, cholinergic interneurons, or autoreceptors on dopamine terminals [D2ARs]). Given the importance of dopamine signaling in the neurobiology underlying or contributing to the development of alcohol use disorders, we sought to determine the effect of ethanol consumption on dopamine release and D2AR function in the DLS. To that end, adult male C57BL6J mice were given ad libitum access to a 10% ethanol solution for four weeks in a two bottle choice ethanol drinking paradigm. Ethanol consumption was recorded throughout the experiment and immediately following the termination of the ethanol access period, we performed fast-scan cyclic voltammetry to measure evoked dopamine release in brain slices of the DLS. Control mice were treated identically except that they received water in both bottles throughout the testing period. To assess D2AR function, we applied the D2DR agonist, quinpirole, to measure inhibition of evoked dopamine release. We also assessed the effect of a one week forced abstinence following the two bottle choice drinking period on our voltammetric measures. The average ethanol consumption across the four week period was 6.3 g/kg/day and the total ethanol intake throughout the experiment was similar between the ethanol-treated groups. We also measured and compared the average body weight increases over the course of the study between all of the experimental groups and observed no significant differences. There were no differences in evoked dopamine release between treatment groups. We did, however, find that the two bottle choice ethanol experience increased D2AR-mediated inhibition of evoked dopamine release relative to control subjects. This effect was transient and autoreceptor function was restored to control levels following one week of forced abstinence. Given that the no abstinence and abstinence ethanol groups had similar ethanol intake levels, it is likely that the observed differences between these two groups are due to the effects of abstinence and not to any differences in ethanol exposure. Altogether, our results support the idea that D2ARs are involved in the development of alcohol use disorders.

Disclosures: A.G. Salinas: None. **Y. Mateo:** None. **D.M. Lovinger:** None.

Poster

077. Neural Effects of Ethanol Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant DA035958

NIH grant AA02919

Title: Acute ethanol activates microglia and affects the excitability of ventral tegmental area neurons

Authors: *S. B. WILLIAMS[1], S. S. PISTORIUS[2], E. Q. ANDERSON[1], D. R. CLARKE[1], T. J. CLARK[1], S. HOPE[1], S. C. STEFFENSEN[1]
[1]Brigham Young Univ., Provo, UT; [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Current dogma is that dopamine (DA) transmission is increased by acute ethanol via excitation of DA neurons in the ventral tegmental area (VTA). However, the EC_{50} for ethanol excitation of DA neuron activity is > 100 mM *ex vivo*, which is 10X more than its rewarding level. Alternately, we have shown in multiple reports that VTA GABA neurons are 10X more sensitive to acute ethanol than DA neurons, at least *in vivo*. However, similar to DA neurons, their firing rate appears to be relatively insensitive to ethanol *ex vivo*. Despite the fact that many groups have shown that DA release is enhanced by acute ethanol *in vivo*, the story is mixed *ex vivo*, with some groups showing enhancement, while others inhibition, of DA release in the nucleus accumbens (NAc). Further complicating this story is that ethanol injected directly into the VTA has no effects on DA release in the NAc. Thus, it appears that there is a major discrepancy between ethanol effects *in vivo* vs *ex vivo* and no clear consensus regarding the hypothesis that ethanol enhancement of DA release is due to direct excitation of DA neurons! The aim of this study was to evaluate the role of neuroimmune responses in acute ethanol effects on VTA neurons. We evaluated the effect of ethanol on microglia proliferation and morphology in the VTA and NAc, as well as the effects of cytokines on VTA neuron activity. We found increased microglia and morphological changes in microglia 2 hours following a single *in vivo* exposure to ethanol (2-4g/kg) in the VTA, but not the NAc. We also used standard cell-attached mode electrophysiological techniques to evaluate the effects of select cytokines on VTA neuron firing rate *ex vivo*. We found no change in VTA GABA neuron firing rate in response to the microglia pro-inflammatory cytokine interleukin-6, but an increase in firing rate in response to the microglia anti-inflammatory cytokine interleukin-10. Current studies are underway to investigate the effects of cytokines on synaptic transmission in VTA neurons. These findings suggest that the rewarding effects of ethanol are mediated, at least in part, by cytokines released by activated microglia.

Disclosures: **S.B. Williams:** None. **S.S. Pistorius:** None. **E.Q. Anderson:** None. **D.R. Clarke:** None. **T.J. Clark:** None. **S. Hope:** None. **S.C. Steffensen:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA035958

NIH Grant AA02919

Title: Chemogenetic stimulation of connexin-36 expressing VTA GABA neurons is rewarding

Authors: *S. S. PISTORIUS, ***S. S. PISTORIUS**, J. D. OBRAY, S. B. WILLIAMS, C. L. CARR, D. R. CLARKE, E. Q. ANDERSON, N. D. FLINT, S. C. STEFFENSEN
Brigham Young Univ., Provo, UT

Abstract: A subpopulation of ventral tegmental area (VTA) GABA neurons express connexin-36 (Cx36) gap junctions (GJs). Activation of GJ-mediated electrical coupling between VTA GABA neurons supports brain stimulation reward, and alcohol reward is lowered in Cx36 KO mice due to a hyper-dopamine (DA) state. The aim of this study was to further evaluate the role of a subpopulation of $Cx36^+$ VTA GABA neurons in alcohol reward and dependence. To accomplish this study, we customized a Gq-coupled Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) viral vector to only express in $Cx36^+$ neurons (AAV8.hCx36.hM3D(Gq)-mCherry.WPRE.rBG) in the VTA. The hM3Dq viral vector was infused into male CD-1 GAD GFP mice and male Wistar rats. The animals were then given 10-14 days to recover prior to experimentation. A control virus (AAV9.CB7.CI.mCherry.WPRE.rBG) was used for comparison. We implemented standard cell-attached mode electrophysiology to evaluate the effects of clozapine-n-oxide (CNO; the ligand for DREADDs) on VTA GABA and DA neuronal activity. We performed loose patch experiments to test the effects of CNO on hM3Dq+ GABA neuron firing rate. We found a robust enhancement of VTA GABA neuron firing rate in hM3Dq+ neurons with 20 μM CNO *ex vivo*. Surprisingly, while investigating CNO effects on VTA DA neuron firing rate, we found that CNO activation of hM3Dq+ VTA GABA neurons increased DA neuron activity, suggesting that Cx36+ VTA GABA neurons indirectly modulate local VTA DA neurons. Intraperitoneal CNO (3 mg/kg) also enhanced the firing rate of VTA GABA neurons *in vivo*. In a conditioned-place preference paradigm, hM3Dq-infused animals showed increased preference for the CNO-paired chamber compared to pre-conditioning, suggesting that activation of hM3Dq+ VTA GABA neurons is rewarding. Control animals showed no preference for the CNO-paired chamber

following conditioning. Administration of CNO prevented ethanol consumption (drink-in-the-dark paradigm) in ethanol naïve hM3Dq-injected mice as well as decreased ethanol drinking in ethanol dependent mice injected with hM3Dq compared to controls, suggesting that the reward received from CNO activation of hM3Dq is enough to block ethanol consumption in both naïve and dependent animals. Taken together, these findings support previous studies indicating that enhanced electrical coupling between VTA GABA promotes reward and lowers the hedonic value of ethanol.

Disclosures: S.S. Pistorius: None. **J.D. Obray:** None. **S.B. Williams:** None. **C.L. Carr:** None. **D.R. Clarke:** None. **E.Q. Anderson:** None. **N.D. Flint:** None. **S.C. Steffensen:** None.

Poster

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NIH grant AA02919

Title: Ethanol enhancement of dopamine release in the nucleus accumbens and ethanol reward are mediated by peripheral neuroimmune interactions

Authors: *J. D. OBRAY[1], T. CLARKE[2], E. Y. JANG[4], B. GARCIA[3], A. KLOMP[1], A. RICHARDSON[2], A. PAYNE[2], S. HOPE[3], C. H. YANG[4], J. T. YORGASON[2], S. C. STEFFENSEN[1]
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Abstract: The prevailing view is that enhancement of dopamine (DA) transmission in the mesolimbic DA system originating in the midbrain ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) underlies the rewarding properties of alcohol. Despite the fact that many labs have shown that DA release is enhanced by acute ethanol *in vivo*, the story is mixed *ex vivo*, with some labs showing enhancement, while others inhibition, of DA release in the NAc. Further complicating this story is that ethanol injected directly into the VTA has no effects on DA release in the NAc. The aim of this study was to determine the role of peripheral neuroimmune responses in mediating ethanol enhancement of DA release in the NAc and ethanol reward in male and female rats. Using microdialysis and HPLC, systemic administration of ethanol (0.5-4.0 g/kg) markedly enhanced DA release in the NAc in male subjects, but produced a biphasic response in female subjects characterized by relatively reduced ethanol

enhancement of DA release followed by a latent decrease in DA release. Ethanol (IP) or IV DA enhancement of DA release in the NAc was abolished by administration of the peripheral-only acting D2 receptor (D2R) antagonist domperidone. Systemic administration of ethanol or DA markedly enhanced the expression and morphology of D2R-containing microglia in the VTA, but not the NAc, within 2 hrs. While ethanol had no effect on the expression of D2Rs on lymphocytes and monocytes *in vitro*, it enhanced monocyte D2R expression 3 hrs after administration in vivo. A place conditioning paradigm was used to test rats for ethanol preference. Domperidone (1 mg/kg, IP) administered before ethanol conditioning trials was found to prevent acquisition of ethanol conditioned place preference. These findings suggest that ethanol enhancement of DA release and ethanol reward is mediated by a peripheral mechanism involving D2Rs on monocytes/microglia. Ethanol or DA evince relatively rapid changes in brain and blood D2 receptor expression, with blood D2R expression lagging behind brain D2R expression by 1 hr. These results challenge the dogma regarding direct ethanol actions on mesolimbic DA transmission. Experiments are ongoing to evaluate ethanol effects on DA release in animal models of monocyte/macrophage/microglia depletion and the role of microglia cytokine release in mediating ethanol effects on DA neurons, DA release and ethanol reward.

Disclosures: **J.D. Obray:** None. **T. Clarke:** None. **E.Y. Jang:** None. **B. Garcia:** None. **A. Klomp:** None. **A. Richardson:** None. **A. Payne:** None. **S. Hope:** None. **C.H. Yang:** None. **J.T. Yorgason:** None. **S.C. Steffensen:** None.

Poster

077. Neural Effects of Ethanol Use

Location: Halls A-C

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Topic: G.08. Drugs of Abuse and Addiction

Support: ZIA AA000421

FI2GM 120030

Title: Striatal dopamine receptors play a role in the stimulatory and depressive effects of alcohol

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Abstract: Alcohol produces both stimulatory and sedative effects in humans. The clinical literature suggests that people who more intensely experience the stimulant effects of alcohol are more likely to abuse the substance and develop dependency. In animal studies, stimulant and depressive effects of alcohol can be quantified by locomotive activity. Previous research

indicates a role for dopamine receptors in the locomotive effects of alcohol, however, a detailed understanding of the receptor class and localization is unknown. The current study examines the contributions of specific subpopulations of dopamine D2 receptors in modulating the stimulant and depressant effects of alcohol. Using genetically engineered mice lacking D2 receptors on medium spiny neurons (MSNs) in the striatum or D2 autoreceptors on midbrain dopamine neurons, we examined dose-dependent, alcohol-induced locomotion. Compared with littermate controls, MSN D2 knockout mice show a significantly increased locomotor response to alcohol, while the mice lacking D2 autoreceptors are more sensitive to the depressive effects of alcohol. To assess differences in alcohol-induced sedation in each of the mouse lines, we performed the Loss of Righting Reflex (LORR). LORR data show that MSN D2 knockout mice are more resilient to the sedative effects of alcohol, with only 50% of mice losing the righting reflex. Meanwhile, D2 autoreceptor knockout mice lose and regained the righting reflex after a high dose of alcohol similar to control mice. To further explore the rewarding and reinforcing aspects of alcohol in these transgenic mice, we examined intake parameters. MSN D2 knockout mice showed a higher preference for alcohol than controls in a two-bottle choice test and increased seeking in a self-administration paradigm. These results suggest that MSN striatal dopamine D2 receptors may be playing an important role in modulating the behavioral responses to alcohol. This may provide an explanation for the variation in individuals' responses to the stimulant effects of alcohol and the resulting susceptibility to abuse and dependence.

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Poster

077. Neural Effects of Ethanol Use

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Topic: G.08. Drugs of Abuse and Addiction

Title: Event-related potential correlates of attentional capture and response inhibition to alcohol images in social drinkers

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Abstract: The transition from the home to the college environment increases exposure to alcohol, in turn increasing the risk for problem drinking. Reactivity to alcohol cues is thought to play a role in problem drinking, such that repeated associations between alcohol and its rewarding effects may strengthen automatic cue reactivity and decrease cognitive control, resulting in cravings and alcohol-seeking behaviors. However, individuals differ with respect to the magnitude of alcohol-related cue reactivity that they exhibit and less is known about these

individual differences. This study examined event-related potentials (ERPs) to images of alcoholic beverages and non-alcoholic beverages using a Go/No-Go paradigm. ERPs were recorded in 23 college students who identified as social drinkers (5 males, 18 females; mean age = 22.0 years), and completed a Go/No-Go task using images of preferred alcohol images and non-alcoholic (control) beverages images. Self-report measures, including state and trait anxiety, alcohol consumption patterns, impulsivity and reward sensitivity. Behavioral results showed that participants were more accurate in Go vs. No-Go trials. Separate analyses were conducted on the peak latencies and amplitudes of the N2 (frontocentral) and P3 (frontocentral and centroparietal). N2 latency was not modulated by target type (alcohol vs. control) or Go/No-Go status, whereas the P3 peaked earlier for Go trials and for non-alcoholic targets over frontocentral regions. Analysis of N2 amplitudes revealed a significant interaction between trial type (Go vs. No-Go) and target type (alcohol vs. non-alcohol), such that N2 amplitudes were larger for non-alcoholic images, but only during Go trials. P3 amplitudes were not sensitive to target type, but were larger for No-Go vs. Go trials. Exploratory correlational analyses revealed that N2 latencies and P3 amplitudes during alcohol No-Go trials were positively associated with alcohol-related reward sensitivity. Our results suggest that the N2 is sensitive to both behavioral inhibition and attentional capture in the context of a Go/No-Go, while the P3 component is primarily sensitive to behavioral inhibition. Although preliminary, the degree of behavioral inhibition to alcohol No-Go trials may also be influenced by associations between alcohol and its positively rewarding effects.

Disclosures: **A. Zborowski:** None. **N.A. Ceballos:** None. **R. Graham:** None.

Poster

077. Neural Effects of Ethanol Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant 2R01DA021274

NIH Grant R15DA040130

Title: Prolonged alcohol and nicotine exposure suppresses inflammatory markers and stress hormone levels

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Abstract: The present study characterized changes in various biomarkers of inflammation and stress during chronic alcohol self-administration and nicotine exposure in rats. Specifically, adult male Wistar rats were trained to self-administer water or alcohol using a saccharin fading procedure. Once stable alcohol self-administration (10% w/v) was established over 25-30 days, the rats were allowed to self-administer alcohol for an additional 12 days. The rats then received an osmotic pump that delivered nicotine for the remainder of the study (3.2 mg/kg/day). Control animals received a sham surgery. The rats were then allowed to self-administer alcohol for an additional 12 days. Blood plasma was collected prior to and following nicotine exposure to compare time-dependent changes in biomarkers of inflammation (IL-1β, IL-6, and IFN-γ) and stress (ACTH and corticosterone). These markers were analyzed using Luminex xMAP® technology. The results revealed that the rats separated into two groups that displayed high (>20 responses) or low (<10 responses) levels of alcohol intake. Following the first 12 days of alcohol self-administration, the high alcohol intake rats displayed a decrease in inflammatory and stress biomarkers as compared to water controls. The latter effect was further suppressed following nicotine exposure, but only in high alcohol intake rats. In contrast, the rats that displayed low levels of alcohol intake did not display any changes in the inflammatory or stress biomarkers. Our results suggest that chronic intake of high levels of alcohol reduces inflammatory signaling and stress responses, and this effect is magnified by co-exposure to nicotine.

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Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA R01 DA030344-01

Title: Differences in age-related desegregation of sensory systems between long-term marijuana users and controls

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Abstract: Long-term marijuana (MJ) use has been associated with differences in brain structure and function (see review by Filbey et al. 2014). Currently, less is known about how MJ use modifies an individual's large-scale functional brain network organization. We examined the

influence of long-term MJ use on differences in functional brain network organization using data obtained in marijuana using adults. We used a graph-theoretical approach to analyze resting-state functional correlations (RSFC) in long-term MJ users (n=87) and control subjects (n=96), with substantial variability in age (18-55y). In addition to chronic drug use, we examined how usage interacts with another robust effect on functional brain organization, aging. Age has been shown to modify large-scale network organization at rest, where studies in healthy adults showed that increasing age is related to less segregated functional brain systems (e.g., Chan et al. 2014); we examined whether chronic drug use may moderate this pattern.
We constructed each subject's brain network with preprocessed and motion-corrected resting-state fMRI data (5min). Brain nodes defined by a RSFC boundary map (Chan et al. 2014; Wig et al. 2014) were affiliated with a specific RSFC-defined functional brain system (Power et al. 2011). Network edges were represented by Fisher's z-transformed RSFC between each pair of nodes. We observed that the pattern of segregation in sensory-motor systems (i.e., visual, hand/mouth somatosensory-motor, auditory) differed with MJ use, as a function of age. Specifically, increasing age was associated with less segregated sensory systems, and this pattern was greater in users than in controls (age × MJ interaction, F=4.21, p=.04). Further examination revealed that the observed difference was driven by sensory systems desegregating from each other in middle-aged MJ users (sensory-sensory segregation; F=4.95, p=.03). To confirm the age × MJ use effect, we included an independent sample of MJ users from a separate scanning site (n=83, age=18-46y) and additional non-using (control) adults (n=127, age=20-55y). The age × MJ use interaction on sensory-sensory segregation was replicated with this expanded sample. Specifically, when compared to the two control groups, both MJ user groups (independent scan sites) exhibited greater age-related desegregation among their sensory systems (F=5.27, p=.02). Together, the results suggest that long-term MJ use may be associated with an altered pattern of functional brain network organization as a function of age, particularly among sensory-motor systems.

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Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DA032890

NIH DA021409

Title: Behavioral modifications following deletion of type 2 cannabinoid receptors in dopamine neurons

Authors: *E. S. ONAIVI[1], A. CANSECO-ALBA[1], H. ZHANG[2], M. A. CHUNG[1], E. K. DENNIS[1], B. SANABRIA[1], N. SCHANZ[1], H. ISHIGURO[3], Z. LIN[4], S. SGRO[1], C. M. LEONARD[1], E. L. GARDNER[2], J. M. EGAN[5], Z. XI[2], Q.-R. LIU[5,1]
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Abstract: Cannabinoid CB2 receptors (CB2Rs) are expressed in mouse brain dopamine (DA) neurons and are functionally involved in several DA-related and other CNS disorders including drug addiction in rodent models. However, the cellular mechanisms underlying this modulation are unclear since the currently available CB2R gene knockout mice are constitutive gene knockout. In addition, both partial N-terminal and C-terminal CB2R-KO mice express truncated CB2R peptides with residual function. Therefore, we generated *Cnr2*-floxed mice that were crossed with DAT-*Cre* mice, in which the recombinase expression is under dopamine transporter gene (DAT) promoter control to generate CB2R conditional knockout mice in midbrain DA neurons in DAT-*Cre*-*Cnr2*-Lox transgenic mice. By using a novel highly-sensitive RNAscope *in situ* hybridization method, we detected clear CB2R mRNA expression in VTA DA neurons in wildtype control and DAT-*Cnr2* heterozygous mice, but not in the homozygous DAT-*Cnr2* cKO mice. We then characterized the DAT-*Cnr2* cKO mice in a battery of behavioral test systems. Here we report that the deletion of CB2Rs in dopamine neurons enhances motor activities, modulates anxiety-like and depressogenic-like behaviors and reduces the rewarding properties of alcohol and cocaine. Our data also reveals for the first time that CB2Rs are involved in the tetrad assay induced by cannabinoids which had been largely associated with CB1R agonism. The GWAS secondary analysis indicate that the CNR2 gene is associated with Parkinson's disease and substance use disorders. We conclude that CB2Rs in dopaminergic neurons play an important role in the modulation of psychomotor behaviors, anxiety, depression, and pain sensation and in the rewarding effects of alcohol and cocaine.

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Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Support: SERC Grant 150113

Title: Effects of chronic CB1 agonist administration on coping with multiple reward devaluations

Authors: *S. E. CONRAD[1], D. DAVIS[1], J. B. THOMPSON[1], S. PAPINI[2], M. R. PAPINI[1]
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Abstract: High expression of the cannabinoid CB1 receptor in brain regions significant for emotional learning regulates fear extinction and stress. This experiment examined coping with unexpected reward devaluations following chronic cannabinoid administration. Rats were injected with WIN 55,212-2 (10 mg/kg, ip), a CB1 receptor agonist, or vehicle (70% DMSO, 30% saline) for 7 consecutive days prior to testing in two reward devaluation tasks. In the consummatory successive negative contrast (cSNC) task, rats were given access to either 32% or 4% sucrose for ten 5-min sessions and then 4% sucrose during sessions 11-13. Rats exposed to a 32-to-4% sucrose devaluation exhibited transient consummatory suppression—the cSNC effect. In the Pavlovian autoshaping (AS) task, the same rats received 3 sessions of AS training with one lever (right or left, counterbalanced) paired with 12 pellets and the other with 2 pellets, for 6 single-lever trials per session. On session 4, the 12-pellet lever was downshifted to 2 pellets and the 2-pellet lever remained unshifted. This session ended with a nonreinforced choice trial with both levers. In the choice trial, animals tend to prefer the unshifted lever (or avoid the devalued lever). Finally, all subjects received two 5-min sessions of open field (OF) testing to assess anxiety in lighted and dark boxes (order counterbalanced). To assess that any effects were due to downregulation of CB1 receptors, the entire sequence was repeated in the absence of WIN. There was modest evidence that chronic WIN shortened cSNC. However, animals previously exposed to a 32-to-4% sucrose downshift in the cSNC task (but not 4% unshifted controls) exhibited a preference for the downshifted lever (rather than the nonshifted lever, as in the other groups). There were no WIN-induced differences in OF testing, and all aforementioned effects were ameliorated or eliminated by repeating testing with no WIN administration. Negative events occurring during downregulation of CB1 receptors impaired coping with additional reward devaluations, a finding that has implications for chronic marijuana users.

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Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Title: Acute drug consumption and motor vehicle collision: A systematic review of 96 cases in Japan 2012-2014

Authors: *S. KANEKO
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Abstract: From 2012 to 2014 in Japan, a total of 214 cases of motor vehicle collisions were attributed to the use of illegal drugs by drivers. In 93 out of 96 investigated cases, the causative agents were 22 kinds of synthetic cannabinoids (SCs). Those SCs can be grouped into three groups according to the timeline of use and their chemical structures. The first generation SC naphtoylindole derivatives, such as MAM-2201, were used in 2012 and disappeared by governmental inclusive, structure-based regulation in 2013 spring. Instead, quinolinyl ester indoles (second generation SC, such as 5F-PB-22) and indazole carboxamides (third generation SC, such as 5F-AB-PINACA) appeared thereafter with much stronger potencies for human CB1 receptor. An outbreak of SC occurred in 2014 summer with the one of the strongest SCs, 5F-ADB. The common signs observed in the SC-abused drivers are impaired consciousness, anterograde amnesia, catalepsy with muscle rigidity, tachycardia, and vomiting or drooling. Since the third generation SCs are extremely potent CB1 agonists (only small amount is required) and instable in blood, it is very difficult to detect SCs in biological samples. Actually, only in one third cases, SC could be detected in blood or urine.

Disclosures: S. Kaneko: None.

Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA033877

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Title: Effects of adolescent cannabinoid administration on anxiety-like behaviors in adult rats

Authors: A. D. HARDIN, V. GOMEZ, M. J. STONE, D. O. SANCHEZ, *C. A. CRAWFORD
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Abstract: Medical use of cannabinoids by adults has grown in popularity as state laws have increased legal access. Children and adolescents are also now being treated with medical cannabis usually involving a combination of THC (the primary psychoactive component of cannabis) and the presumed non-psychoactive cannabinoid, cannabidiol (CBD). This

combination is thought to allow the medicinal benefits of THC while protecting against THC-induced psychopathology (i.e., anxiety). Although CBD is anxiolytic in adults, the effects of CBD after adolescent exposure is unknown. Moreover, there is no available data on the combined effects of CBD and THC on affective behavior in adolescents. To this end, we pretreated rats with CP-55,940 (s synthetic THC-like cannabinoid agonist), CBD, a combination of CP-55,940 and CBD (CP/CBD), or vehicle for a short-term (10 days) or chronic (25 days) period and assessed anxiety-like behavior in adulthood. Adolescent male and female Sprague-Dawley rats were injected daily with CP-55,940 (10 μg/kg, sc), CBD (10 mg/kg, sc), CP/CBD (sc), or vehicle (sc) beginning on PD 31 for 10 or 35 consecutive days. On PD 60 and PD 65, anxiety-like behavior was measured using a light/dark box and elevated plus maze, respectively. Testing occurred one hour following daily injections. None of the drug treatments altered behaviors in rats treated for 10 days. In contrast, rats chronically exposed to CBD for 35 days displayed increased-anxiety like behavior because they spent less time in the open arms of the elevated plus maze and in light compartment of the light/dark box as compared to vehicle-treated rats. These results suggest that chronic cannabinoid treatment in adolescent may produce adult-atypical results. In particular, CBD may not be anxiolytic after chronic adolescent exposure and interestingly direct activation of cannabinoid receptors may not induce anxiety in this age group.

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Poster

078. Cannabinoids and Marijuana

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Title: Delta-9-Tetrahydrocannabinol vapor inhalation attenuates oxycodone self-administration

Authors: *J. D. NGUYEN, Y. GRANT, K. M. CREEHAN, M. A. TAFFE
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Abstract: Prescription opioid abuse is a significant global problem, thus the use of non-opioid drugs has been investigated for the treatment of pain and the reduction of adverse effects such as abuse or overdose. The interaction between cannabinoids and opioids has been shown to modulate nociception and positive reinforcing effects in animals. In this study, Δ^9-

tetrahydrocannabinol (THC) and oxycodone were administered to rats and assessed for the possible enhancement of antinociceptive effects. We further investigated the effects of THC vapor inhalation, using electronic-cigarette technology, on oxycodone intravenous self-administration under extended access conditions. Adult Wistar rats were administered vaporized THC (50 mg/mL), oxycodone (100 mg/mL), THC/oxycodone combination or vehicle for 30 minutes and then assessed for tail-withdrawal latency for nociception. Tail-withdrawal latency was increased by THC or oxycodone alone, and latency was significantly higher in rats that were administered the THC/oxycodone combination compared to either drug alone. Similarly, rats that were exposed to injected THC (5.0 mg/kg, i.p.) and oxycodone (2.0 mg/kg, s.c.) in combination showed an additive effect on tail-withdrawal latency. A separate group of male rats was trained to intravenously self-administer oxycodone (0.15 mg/kg/infusion) under a fixed-ratio 1 (FR1) response contingency during an 8 h session. Following acquisition, the rats were administered vaporized (100 or 200 mg/mL) or injected THC (5 or 10 mg/kg, i.p.) or propylene glycol (PG) for 30 minutes prior to oxycodone self-administration. Self-administration in rats exposed to vaporized or injected THC was significantly decreased compared to vehicle-exposed control rats. These data show the combined effects of THC and oxycodone exposure in rats and further demonstrate the interaction of cannabinoids and opioids on nociception and reward. Furthermore, these data suggest the potential use of cannabinoids in combination with opioids for the enhancement of antinociception, while mitigating opioid abuse and dependence.

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Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Support: R21DA039701

McKnight Brain Research Foundation

Title: An apparatus for cannabis smoke self-administration procedures in rats

Authors: *D. T. GUENTHER[1], J. KENNEDY[2], I. VELTCHEV[7], A. W. BRUIJNZEEL[3], M. FEBO[4], B. SETLOW[5], A. P. MAURER[6]
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Abstract: Cannabis is the most widely used illicit drug in the U.S., with 7% of the population reporting current use and an estimated 9% of cannabis users displaying signs of abuse or dependence (Lopez-Quintero et al., 2011; SAMHSA, 2013). With the high prevalence and potential adverse effects of chronic cannabis use (such as cognitive impairments and risk of psychiatric disorders) comes an urgent need to better understand the neural and behavioral mechanisms of cannabis use. The use of animal models in research has been invaluable in advancing our knowledge and understanding of substance use, and indeed, cannabinoid self-administration models have been developed in both monkeys and rodents. While these models have provided the basis for understanding environmental, pharmacological, and hormonal conditions that can regulate cannabinoid intake, they have almost exclusively depended on intravenous routes of delivery. Most people, however, smoke cannabis, which can produce a variety of cannabinoids and other compounds aside from THC, some of which are psychoactive (Vann et al., 2008; Ren et al., 2009; Niesink & van Laar, 2013). Hence, development of an animal model of cannabis smoke self-administration could have the potential to more closely model the circumstances of actual human cannabis use. Prior data, including some from our laboratories, show that passive exposure to cannabis smoke produces dependence and withdrawal symptoms similar to those observed with administration of THC or other cannabinoid receptor agonists (Tanda et al., 2000; Fattore et al., 2001; Wilson et al., 2006; Panlilio et al., 2010; Bruijnzeel et al. 2016). The goal of the current project was to develop and validate equipment and procedures for cannabis smoke self-administration in rats. An apparatus was designed and constructed to provide response-contingent ("burn-on-demand") delivery of cannabis smoke. This apparatus is integrated with an operant chamber equipped with a sniffing port, into which both the cannabis smoke and a liquid food reward can be delivered. Initial data indicate that rats' responding for food reward at the sniffing port is not reduced by concurrent delivery of cannabis smoke in non-food-deprived rats (i.e., the smoke is not sufficiently aversive to dissuade rats from seeking the food reward). Ongoing experiments are determining whether cannabis smoke is sufficiently reinforcing to maintain responding in the absence of food reward.

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Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant R21DA039349

Title: Lasting effects of adolescent exposure to cannabis smoke on measures of affect and cognition in rats

Authors: *A. W. BRUIJNZEEL[1], P. KNIGHT[1], S. PANUNZIO[1], S. XUE[1], M. M. BRUNER[2], S. WALL[2], M. FEBO[1], B. SETLOW[1]
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Abstract: Cannabis is the most widely used illicit drug in the US, and cannabis use among adolescents continues to rise. Some studies suggest that adolescent cannabis use increases the risk for depression, anxiety, and cognitive impairments later in life. In addition, animal studies show that chronic administration of high doses of delta 9-tetrahydrocannabinol (THC) or synthetic cannabinoid agonists during adolescence can have detrimental effects in adulthood. Because smoking is the primary route of THC self-administration in humans, however, we investigated the long-term effects of adolescent cannabis smoke exposure in a rat model. In our previous work, we established a whole body cannabis smoke exposure protocol, in which exposure to cannabis smoke in adult rats leads to the development of dependence. In the present study, adolescent rats were exposed to cannabis smoke, which models human cannabis smoking. A control group was exposed to placebo smoke, which was generated by burning cannabis cigarettes from which cannabinoids were extracted. Cannabis cigarettes (5.8% THC) and placebo cigarettes were obtained from NIDA and cannabis smoke was generated using an automated cigarette smoking machine. We exposed male and female rats to either cannabis smoke, placebo smoke (cannabis plant material without THC), or air control conditions from P29-P50 (n = 6/sex/group). When the rats reached adulthood (P70) we investigated their behavior in a large open field (120 x 120 cm), elevated plus maze test, sucrose preference test, forced swim test, and novel object recognition test. In the large open field test, there was no effect of sex or smoke exposure condition on locomotor activity. In the elevated plus maze test, there was a main effect of exposure condition on percentage of open arm entries (open arm entries/total arm entries) and percent time in the open arms (time on open arms/ total time on open and closed arms). This effect was mainly due to a decrease on both measures in rats exposed to cannabis smoke compared to the air control group, suggesting a potential increase in anxiety-like behavior. There was no effect of sex or smoke exposure on sucrose consumption or behavior in the forced swim test. In the novel object recognition test, neither sex nor exposure condition affected performance (discrimination index, calculated as: (Time Novel -Time Old)/(Time Novel + Time Old)). In conclusion, these preliminary findings suggest that exposure to cannabis smoke may increase anxiety-like behavior but does not affect depressive-like behavior or cognitive function.

Disclosures: A.W. Bruijnzeel: None. **P. Knight:** None. **S. Panunzio:** None. **S. Xue:** None. **M.M. Bruner:** None. **S. Wall:** None. **M. Febo:** None. **B. Setlow:** None.

Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 078.09/OO16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA041464

Title: Lesion of the rostromedial tegmental nucleus facilitates acquisition of delta-9-tetrahydrocannabinol self-administration

Authors: *S. M. SPENCER[1], H. LI[2], D. SCHWARTZ[2], T. C. JHOU[2], P. W. KALIVAS[3]
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Abstract: Marijuana is the most widely used illicit drug in the world. Yet when the rewarding properties of the primary psychoactive constituent of the drug, delta-9-tetrahydrocannabinol (THC) have been directly tested in rodent taste and place conditioning paradigms, largely avoidant or aversive reactions have been reported. In humans the most common negative side effects of acute marijuana consumption especially in drug naïve or occasional users are anxiety and paranoia, which can be overcome with repeated drug use. Thus in humans it is believed that the transition from recreational drug use to drug dependence for marijuana coincides with the progressive shift of the rewarding properties coming to predominate over the drug's aversive effects. Likewise in in some studies THC pre-exposure alleviates the aversive effects of the drug and may unmask its reinforcing properties. We have developed a THC self-administration procedure that incorporates a vapor pre-exposure period prior to initiating drug taking. The rostromedial tegmental nucleus (RMTg) has been implicated in regulating the balance of reward and aversion for other abused substances; therefore, we hypothesized that this brain region might be involved in THC reward. As an initial investigation into this hypothesis we assayed for cfos activation in RMTg following THC-primed reinstatement in rats previously trained to self-administer THC + cannabidiol (CBD), and found that cfos counts were increased in reinstated rats compared to extinction controls. We also performed excitotoxic lesions of the RMTg in male Sprague-dawley rats and assessed the de novo acquisition of THC + CBD self-administration compared to rats with sham lesions. Lesioning the RMTg facilitated the acquisition of THC self-administration. In ongoing studies, we will evaluate whether RMTg lesions facilitate reinstated drug seeking following extinction, and continue to interrogate differential patterns of brain cfos activity at various stages of THC taking and seeking.

Disclosures: S.M. Spencer: None. **H. Li:** None. **D. Schwartz:** None. **T.C. Jhou:** None. **P.W. Kalivas:** None.

Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 078.10/OO17

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA003906

Title: Regulation of cue-induced THC seeking in the nucleus accumbens

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Abstract: Marijuana is the most widely used illicit drug in the United States. Thus, there is a demand for further research to understand the neurobiological effects of cannabis. Our lab has recently established a rodent model of operant Δ^9-tetrahydrocannabinol + cannabidiol (THC+CBD) self-administration. With this model, we can examine the neuroadaptive mechanisms underlying daily THC+CBD use and relapse to drug-associated cues. We previously found that cocaine cue-induced relapse involves transient-synaptic potentiation (t-SP) at glutamatergic synapses on medium spiny neurons (MSNs) in the nucleus accumbens. t-SP is initiated by spillover of synaptically released glutamate from cortico-accumbens synapses to stimulate neuronal nitric oxide synthase (nNOS) interneurons and the release of nitric oxide. It is unknown whether this cascade of events necessary for cue-induced cocaine seeking also mediates cue-induced THC+CBD seeking. Here, we hypothesize that pharmacological antagonism of nNOS by microinjecting N-propyl-L-arginine (NPLA) into the accumbens attenuates cue-induced reinstatement. We pretreated male Sprague-Dawley rats with NPLA (0.1 nmol) or vehicle 10 minutes prior to the reinstatement test and observed inhibited cue-induced reinstatement in NPLA-treated rats. The role of nNOS in cue-induced THC+CBD seeking supports the likelihood that like all other addictive drugs tested to date, the desire to seek and use marijuana activates an intra-accumbens microcircuit involving nNOS interneurons.

Disclosures: V. Chioma: None. **P. Kalivas:** None.

Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 078.11/OO18

Topic: G.08. Drugs of Abuse and Addiction

Support: DA016511

Title: Changes in synaptic metaplasticity after extinction from drug self-administration and cue induced relapse - A comparison between THC, cocaine and heroin

Authors: *D. NEUHOFER[1], S. M. SPENCER[2], V. CHIOMA[3], D. SCHWARTZ[1], P. W. KALIVAS[4]
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Abstract: Glutamatergic plasticity in the nucleus accumbens (NAc) is a key neuronal substrate of appetitive learning that allows adaptive behavioral responding to changing environmental contingencies. Consequently, dysfunction in the expression of synaptic plasticity parallels behavioral deficits in many murine models of neuropsychiatric diseases, including addiction. One form of impaired plasticity associated with chronic drug use is loss of a postsynaptically expressed NMDA-dependent LTD induced by a low frequency pairing protocol (i.e. 1-5 Hz stimulation + depolarization of the postsynaptic cell to -50 mV) in NAc medium spiny neurons (MNSs). In vivo and in vitro LTD is abolished after withdrawal or extinction from cocaine self-administration, and in vivo after extinction from heroin self-administration. These studies indicate that, despite the different neuroadaptations caused by chronic heroin or cocaine, both drugs induce similar impairments in synaptic plasticity. Using a novel model of THC+CBD self-administration we show that THC+CBD impairs synaptic plasticity akin to other addictive drugs, suggesting these impairments may be a generalizable mechanism in drug addiction. Second, we show that the loss of LTD is restored by presenting cues previously associated with drug use, a novel finding revealing involvement of transient metaplasticity in drug seeking behavior.Experiments are underway that examine which neuroadaptations mediate cortico-accumbens metaplasticity following THC+CBD self-administration and cue induced reinstatement. Moreover we are exploring how metaplasticity affects reinstated drug seeking. Finally we are determing whether the newly discovered rescue of NMDA-dependent LTD is specific for THC+CBD cue induced reinstatement or applies also to other drugs of abuse.

Disclosures: D. Neuhofer: None. **S.M. Spencer:** None. **V. Chioma:** None. **D. Schwartz:** None. **P.W. Kalivas:** None.

Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 078.12/OO19

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Intramural Research Program

Title: Pathway-specific synaptic plasticity of glutamatergic transmission in the nucleus accumbens caused by the psychoactive marijuana constituent, delta-9-tetrahydrocannabinol

Authors: *E.-K. HWANG, C. R. LUPICA
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Abstract: Cannabis is the most widely used illicit drug and its use is often associated with psychiatric disorders. THC is an agonist of cannabinoid 1 and 2 receptors (CB1R, CB2R), through which it acts on brain reward systems to increase dopamine (DA) neuron activity and DA release. All DA neurons express tyrosine hydroxylase (TH), and a subpopulation also expresses a vesicular glutamate transporter (VGluT2), permitting co-transmission of DA and glutamate. Axons of DA/glutamate neurons originating in the ventral tegmental areas (VTA) project to the medial NAc shell, although the physiological and behavioral consequences of co-release is not fully understood. We have shown that CB1Rs increase DA neuron excitability in the VTA and alter synaptic processes in the NAc, and we further hypothesize that THC can modify glutamate transmission in this pathway. Here, we used THCre transgenic rats to express channelrhodopsin-2 (ChR2) in DA neurons in the VTA and dorsal raphe (DR), and we isolated ChR2-evoked AMPA receptor-mediated glutamate EPSCs arising from these pathways in NAc neurons in vitro. Rats were injected once per day, with THC (5 mg/kg), THC + a CB1R antagonist (AM251), or vehicle for 13-15 days, and brain slices were obtained 1d following the final injection. Chronic THC caused a decrease in the strength of electrical stimulation-evoked glutamate inputs to neurons in the medial NAc shell, with no change in GABAergic transmission, indicating a decreased excitation-inhibition ratio. In contrast, the relationship between light intensity and ChR2-evoked EPSC amplitude was not altered in the VTA-NAc pathway, but the number of AMPA receptors containing GluR2 subunits was decreased. Chronic THC also increased glutamate release probability in the VTA-NAc pathway, and all effects were prevented by AM251. In contrast, chronic THC had no effect on EPSC properties evoked by ChR2-activation of the DR-NAc pathway. In conclusion, chronic THC caused pathway-specific, homeostatic scaling of plasticity of DA neuron-evoked EPSCs through AMPA receptor subunit redistribution and increased probability of glutamate release. These results suggest that chronic marijuana use may selectively alter DA/glutamate co-transmission in the mesoaccumbens reward pathway.

Disclosures: E. Hwang: None. **C.R. Lupica:** None.

Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant DA032890

CONACYT grant CVU332502

Title: Role of cannabinoid type 2 receptors in brain dopamine neurons in the rewarding effects of psychostimulants, alcohol and cannabinoids in DAT-Cnr2 conditional knockout mice

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Abstract: The dopaminergic mesocorticolimbic system (MSL), originate in the ventral tegmental area (VTA) and project mainly to the nucleus accumbens and the prefrontal cortex, brain areas that are involved in the rewarding effects of drugs of abuse. Endocannabinoids (eCB) are retrograde signaling molecules that modulate the MSL activity through the activation of the cannabinoid receptors, CB_1R and CB_2R. VTA eCB receptors, have been suggested to play a key role in the regulation of motivation, therefore eCB play an important role in the regulation of rewarding behaviors through the modulation of MSL activity. Cannabinoid receptors are involved in the modulation of the rewarding properties of psychostimulants and a number of studies have focused on the role of CB_1R in drug addiction with less attention on CB_2R. However, accumulating evidence now show the presence and functional role of CB_2R in the central nervous system and have recently been reported to modulate brain dopamine-related behaviors. It has also been suggested that CB_1R and CB_2R may play opposite roles in the regulation of the reinforcing properties of drugs of abuse. The post-synaptic localization of CB_2R in some brain areas has been reported and the activation of these receptors inhibiting VTA dopamine neuronal firing have been demonstrated. The objective of this work was to further characterize the role of CB_2R in the rewarding proprieties of different drugs. To this aim, we evaluated the rewarding properties of the selected drugs using the conditioned place preference model (CPP) and the alcohol preference test in the DAT-*Cnr2* conditional knockout (cKO) mice that do not express the CB_2R in midbrain dopamine neurons. We found that the DAT- *Cnr2* cKO animals are resistant to the induction of CPP caused by cocaine, alcohol and WIN 55212, a CB_1 and CB_2 cannabinoid receptor mixed agonist. We also found that the DAT-*Cnr2* cKO mice did not show preference to alcohol consumption in comparison with the C57BL/6J control mice. We concluded that CB_2 receptors in dopaminergic neurons plays a role not only in the rewarding properties of cocaine, but also in that of alcohol and the WIN 55212-2 compound.

Disclosures: A. Canseco-alba: None. **E. Dennis:** None. **M. Chung:** None. **B. Sanabria:** None. **N. Schanz:** None. **H. Ishiguro:** None. **Q. Liu:** None. **E.S. Onaivi:** None.

Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 078.14/OO21

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH

NIDA

Title: Chronic passive exposure to cannabis smoke leads to affective withdrawal signs and dependence in rats

Authors: *A. RAVULA[1], H. CHANDASANA[1], S. WALL[2], B. SETLOW[2], M. FEBO[2], A. BRUIJNZEEL[2], H. DERENDORF[1]
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Abstract: Cannabis is the most widely used illicit drug in the US, and cannabis use among young adults continues to rise. Previous studies have shown that chronic systemic administration of delta 9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, or cannabinoid type 1 (CB1) receptor agonists leads to the development of dependence. However, because smoking is the most popular route of THC self-administration it is critical to investigate the effects of cannabis smoke inhalation. The goal of the current study was to investigate if cannabis smoke inhalation leads to the development of cannabis dependence in rats. Cannabis cigarettes (5.6% THC) were obtained from NIDA and smoke was generated using an automated cigarette smoking machine. Drugs of abuse are used for their hedonic effects, which can be assessed in animals as facilitation of brain stimulation reward during electrical intracranial self-stimulation (ICSS). Drugs that potentiate brain reward function decrease ICSS thresholds, and withdrawal leads to increases in thresholds (thought to reflect dysphoria). Male Wistar rats were exposed to cannabis smoke or room air for 50 or 100 min/day, 5 days/week for 4 weeks. Based on our previous work with cannabis smoke (Bruijnzeel et al., 2016), it was expected that two weeks of smoke exposure would lead to dependence. Therefore, the CB1 receptor antagonist rimonabant (0.3, 1, 3 mg/kg, i.p.) was administered acutely during weeks 3 and 4 to investigate the development of dependence. Plasma samples were collected 30 min after completion of smoke exposure on days 4 and 11, and were analyzed using LC-MSMS. THC levels at this time point were 6.51 ± 3.13 and 6.82± 2.90 ng/ml for the 50 and 100 min exposure groups, respectively. Chronic exposure to cannabis smoke alone did not affect baseline ICSS thresholds. Acute administration of rimonabant induced a dose-dependent increase in ICSS thresholds in the cannabis smoke-exposed rats, but had no effects on ICSS thresholds in the control rats. These findings indicate that chronic cannabis smoke exposure can lead to dependence, as indicated by rimonabant-precipitated affective withdrawal signs. This finding is consistent with the fact that

cannabis users experience tolerance to the drug's hedonic effect, and dysphoria upon cessation of cannabis use. Taken together, this animal model can be used to compare the effects of THC and other cannabinoids, characterize development of dependence, and may contribute to the development of new treatments for cannabis use disorders in humans.

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Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 078.15/OO22

Topic: G.08. Drugs of Abuse and Addiction

Title: Subcortical functional hyperconnectivity in cannabis dependence

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Abstract: Cannabis use has been associated with higher risk of psychosis (including schizophrenia), particularly for frequent use and early cannabis initiation. However, the mechanisms underlying this association are poorly understood. Because increased DA signaling in midbrain-striatal circuits is associated with psychoses, we hypothesized that regular cannabis abuse (CA) would be associated with increased resting functional connectivity in these circuits. To test this hypothesis, we took advantage of the large dataset produced by the Human Connectome Project and examined resting brain activity of subcortical regions in 441 young adults, including 30 CA meeting DSM criteria for dependence, and 30 controls matched on age, sex, education, BMI, anxiety, depression, and alcohol/tobacco usage. Across all subjects, local functional connectivity density (lFCD) hubs were most prominent in ventral striatum, hippocampus, amygdala, dorsal midbrain, and the posterior-ventral brainstem. As hypothesized, CA showed markedly increased lFCD relative to controls in ventral striatum and substantia nigra/ventral tegmental area but also in brainstem and lateral thalamus. These effects were observed in the absence of significant differences in subcortical volume, and were most pronounced in the individuals who began cannabis use earliest in life. Behaviorally, the groups did not significantly differ on various metrics of cognitive performance. However, in line with previous research, CA reported higher levels of negative emotionality, which was associated with higher levels of subcortical lFCD in CA but not controls. Together, these findings suggest that chronic cannabis abuse is associated with changes in resting brain function, particularly in dopaminergic nuclei implicated in psychosis but that are also critical for habit formation and reward processing. These results shed light on neurobiological differences that may be relevant to the increased risk for psychoses associated with cannabis use.

Disclosures: **P. Manza:** None. **D. Tomasi:** None. **N.D. Volkow:** None.

Poster

078. Cannabinoids and Marijuana

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA033877

NIH Grant GM100829

Title: Effects of adolescent cannabinoid exposure on young adult nicotine reward

Authors: *J. L. RAZO, A. E. MORAN, V. GOMEZ, D. O. SANCHEZ, C. A. CRAWFORD
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Abstract: Adolescent exposure to nicotine alters the response to several addictive drugs in adult rodents. Specifically, adolescent nicotine treatment potentiates the reinforcing value of alcohol, cocaine, and methamphetamine and decreases the aversive qualities of cocaine. Recently we found that adolescent nicotine exposure increased the conditioned rewarding effects of the cannabinoid agonist CP 55,940. These data are supportive of the gateway theory of addictive substances which postulates that there is a sequence and progression in substance use from tobacco, to alcohol, to illicit drug use. Interestingly, there is also evidence suggesting that cannabis use leads to a reverse gateway where cannabis use leads to greater nicotine use. Specifically, it has been reported that high rates of cannabis use (weekly or greater) in non-tobacco smoking adolescents is predictive of later tobacco use. To this end, we exposed rats with CP-55,940 throughout the adolescent period and later assessed nicotine-induced conditioned place preference (CPP) in adulthood. Male and female Sprague-Dawley rats were injected with CP-55,940 (0, 10, 20, or 30 µg/mg, sc) daily beginning on postnatal day (PD) 31. CP-55,940 injections continued until the end of CPP experiment. On PD 60, nicotine-induced CPP was assessed using a 10-day biased CPP procedure, consisting of one preconditioning day, 10 conditioning days and one test day. Rats were pre-exposed to nicotine (0.16, 0.32, or 0.64, ip) on the preconditioning day. The dose of nicotine used on the preconditioning day was also used on the conditioning days. Preference for the nicotine-paired room was determined by subtracting the time the rat spent in the room before pairing from the time spent on the test day. Rats treated with CP-55,940 (10 µg/kg) spent more time in the generally less-preferred white compartment on the preconditioning day as compared to vehicle treated rats. On the test day, female but not male rats conditioned with nicotine (0.16 mg/kg) had a greater preference score than rats conditioned with vehicle or 0.64 mg/kg nicotine. Preference for the nicotine-paired compartment also varied by cannabinoid treatment. Specifically, rats pretreated with CP-55,940 (10 µg/kg)

and conditioned with 0.64 mg/kg nicotine had greater preference scores for the drug-paired compartment as compared to rats pretreated with vehicle and conditioned with the same dose of nicotine. These findings suggest that adolescent exposure to a cannabinoid can enhance the rewarding value of nicotine.

Disclosures: **J.L. Razo:** None. **A.E. Moran:** None. **V. Gomez:** None. **D.O. Sanchez:** None. **C.A. Crawford:** None.

Poster

078. Cannabinoids and Marijuana

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 078.17/OO24

Topic: G.08. Drugs of Abuse and Addiction

Title: Endocannabinoid regulation of operant responding to predictive incentive cues for a sucrose reward

Authors: *A. N. BAINDUR[1], K. T. WAKABAYASHI[1,2], M. FEJA[1], K. CHEN[1], A. K. SHIELDS[1], M. J. NIPHAKIS[3], B. CRAVATT[3], C. E. BASS[1]
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Abstract: The endocannabinoid system in the ventral tegmental area (VTA) regulates cue-induced responding for food and drug reinforcers. For example, antagonists to the CB1 receptor (e.g. rimonabant) block responding for food and drug reinforcers, as well as cue-induced reinstatement. More recently, it has been shown that indirect enhancement of 2-arachidonyl glycerol (2-AG) signaling increases breakpoints for intra-cranial self-stimulation under a progressive ratio (PR) schedule. The monoacyl glycerol lipase (MAGL) inhibitor, JZL-184 was used to block degradation of 2-AG. Yet JZL-184 had no effect on nicotine self-administration under fixed or PR schedules, although it potentiated cue-induced reinstatement. We have further evaluated the role of endocannabinoid signaling in an incentive cue task. When neutral cues are repeatedly paired with a reward, they can develop powerful incentive properties. In this task, Long Evans rats were exposed to an intermittent 8 second audiovisual cue presented approximately every 30 seconds for 1 hr, where a successful nosepoke during the cue resulted in delivery of sucrose (60 μl) into a reward cup. We evaluated the response ratio (the number of successful responses/predictive cues), the latency to nosepoke in response to the cue, and the latency to enter the reward cup. Rimonabant dose-dependently (1, 3, and 6 mg/kg dose, i.p.) decreased the response ratio while increasing the latency to nosepoke. However, the latency to enter the reward cup was unchanged. These data indicate that the CB1 receptor mediates responding to and motivation for the incentive cue but has little effect on the motivation to consume the reinforcer. We hypothesized that the ability of rimonabant to disrupt incentive cue

responding resulted from blocking 2-AG signaling and that increasing 2-AG levels would therefore enhance responding. However, rats on this task generally respond to ~80-90% of the cues, thus we modified the task so that the volume of reinforcer decreased every 15 min over the 1 hr, from 60, 40, 20 to 10 µl, which produced a corresponding decrease in response ratio within session. We then pretreated with MJN110 (5 mg/kg, i.p.) which is a more selective inhibitor for MAGL, and more potent at raising brain levels of 2-AG compared to JZL-184. MJN110 increased response ratios across sucrose volumes. Together these results indicate that 2-AG signaling through the CB1 is a critical component regulating the responding to incentive cues. Further studies will define whether these effects occur through VTA CB1 signaling, and if so on which neuronal populations.

Disclosures: A.N. Baindur: None. **K.T. Wakabayashi:** None. **M. Feja:** None. **K. Chen:** None. **A.K. Shields:** None. **M.J. Niphakis:** None. **B. Cravatt:** None. **C.E. Bass:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.01/OO25

Topic: G.08. Drugs of Abuse and Addiction

Support: UCONN PCLB Psychological Sciences Undergraduate Research Grant

The Connecticut Institute for the Brain and Cognitive Sciences Seed Grant

Title: Nicotine effects on conditioning, extinction, and reinstatement in humans using virtual reality

Authors: *A. PALMISANO
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Abstract: In addition to acting as a primary reinforcer, nicotine has been shown to enhance the reinforcement and reward-responsiveness of non-nicotine stimuli. To date, few studies have examined nicotine's ability to enhance the value of reward in humans using a conditioned place preference (CPP) paradigm. The present study sought to examine the ability of nicotine to enhance human preference for a virtual environment paired with a chocolate food reward, using a novel virtual reality CPP task. We also sought to determine whether nicotine slows the rate of extinction for previous conditioning in humans as it appears to do in nonhuman species, and investigated whether nicotine increases reward-primed reinstatement after extinction. In this two-day study, nicotine-experienced participants with varying levels of dependence explored two virtual rooms where they received pairings of M&M rewards in one room, and no rewards in the other room, followed by a free-access test session in the absence of rewards. On day two,

participants received several test sessions to assess extinction, and then received M&Ms in a novel context and were tested for reinstatement. Prior to testing on each day, subjects were administered either nicotine (4 mg) or placebo lozenges, in a four-group, 2x2 design (nicotine or placebo on days 1 and 2). We found that after conditioning on day one, only participants who received placebo exhibited a CPP by spending more time in the room previously-paired with M&Ms. However, post hoc analysis indicated that in a subset of participants with greater nicotine dependence (as determined by the Fagerstrom Test for Nicotine Dependence), the nicotine group rated the M&M-paired room more favorably than those who received placebo ($p < 0.05$). Additionally, those who received nicotine on Day 2 spent significantly more time in the previously-paired M&M room during the last extinction session ($p < 0.01$), and exhibited significantly greater reinstatement compared to placebo-treated participants ($p < 0.05$). Taken together, these findings partially support preclinical evidence that nicotine can affect learning, extinction, and reinstatement. To our knowledge, this is the first time that the effects of nicotine on CPP have been examined in humans demonstrating the efficacy of utilizing the virtual CPP paradigm to help understand the behavioral mechanisms of substance dependence. Moreover, these data provide a solid foundation for future studies aimed at more thoroughly characterizing the reward mechanisms that underlie risks for maintaining nicotine use, as well as risks for relapse following cessation.

Disclosures: A. Palmisano: None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.02/OO26

Topic: G.08. Drugs of Abuse and Addiction

Support: the Youth 1000 Talent Program of China

Title: 20 Hz repetitive magnetic stimulation (rTMS) greatly improved smoking cessation and reduced brain entropy: A pilot study

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Abstract: Aims: Smoking is difficult to quit because of the high relapse rate. Imaging studies showed that smoking impairs brain functions in prefrontal cortex and increases brain activity

irregularity as measure by brain entropy (BEN). The purpose of this study is to examine whether smoking cessation can be improved by modulating frontal brain activity using high-frequency repetitive transcranial magnetic stimulation (rTMS) and whether that improvement is coincident with BEN reduction.
Methods: 14 treatment-seeking smokers were offered a program of 10 days rTMS treatment (T10) and 25 days follow-up (F25). rTMS treatment started after 24 hours abstinence from smoking. 20 Hz rTMS was applied on left dorso-lateral prefrontal cortex and the superior medial frontal cortex. At each daily rTMS treatment session, each site received 1000 pulses with a magnitude adjusted to be 90% of the resting motor threshold. Carbon monoxide (CO) level, withdrawal, and craving scales were collected daily during T10 and several times randomly during F25, and again at the end of F25. Neuroimaging data were collected at the baseline, after T10, and F25.
Results: Ten smokers (>10 cigarettes per day, Fagerstrom score>5, years of smoking>8, times of quitting attempts>3) finished the entire treatment program. 8 didn't smoke during the entire 35 days; one relapsed because of non-cooperation; the other one didn't smoke at all after day 5. Withdrawal and craving were the same after T10 and F25, both were significantly ($p<0.05$) reduced compared to baseline. Two subjects were followed up for 6 months and were able to keep abstinence. Overall, there was a 90% smoking cessation rate at day 36 by self-report, verified by CO (or urine) testing. Resting BEN was significantly ($p<0.01$, $n=5$) reduced at the end of treatment, consistent with the finding of lower entropy in non-smokers (vs. smokers), in our recent publication.
Conclusions: 20 Hz two site rTMS produced a high smoking cessation rate, which was paralleled by reduced withdrawal and craving scales, as well as reduction in resting state brain entropy. These pilot findings need further confirmation, both with 'sham' stimulation and larger sample size.

Disclosures: W. Peng: None. **D. Chang:** None. **J. Zhang:** None. **Q. Ge:** None. **Z. Shen:** None. **X. Gao:** None. **J. Ying:** None. **Y. Du:** None. **Z. Zhao:** None. **A.R. Childress:** None. **Z. Wang:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.03/OO27

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA038843

Title: Positive modulation of adenosine A_{2A} receptors reduces nicotine self-administration in rats

Authors: S. G. MALONE[1], J. M. GOLSON[1], C. A. BRADLEY[2], R. W. BROWN[3], C. S. BAILEY[1], *M. I. PALMATIER[2]
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Abstract: Adenosine A_{2A} receptors (A_{2A}Rs) form a heteromeric complex with dopamine D_2 receptors (D_2Rs), primarily in the striatum, and A_{2A}R agonists allosterically decrease D_2R affinity. Nicotine self-administration (NSA) activates D_2Rs by quantal release of dopamine in the ventral striatum and NSA increases expression of high affinity D_2Rs in the ventral striatum. We hypothesized that increasing adenosine A_{2A}R activity with an agonist CGS 21680 (CGS) or an adenosine kinase inhibitor ABT-702 (ABT), would reduce nicotine self-administration. Rats (n=10) were instrumented for intravenous nicotine self-administration and allowed to self-administer nicotine (30 ug/kg/infusion, base) under an FR 5 schedule of reinforcement. After responding stabilized, we began pretreatment tests with ABT (15-180 ug/kg, IP, 60 min before testing) and CGS (30-180 ug/kg, IP, 15 min before testing). Each drug pretreatment test was followed by a 48 h 'washout' and a saline pretreatment test; there was no evidence of a change in baseline on these tests. Following the final CGS tests, we conducted a chronic treatment phase; the 30 ug/kg dose of CGS was administered over 4 consecutive tests to half of the rats (n=5) and a saline was administered to a control group (n=5). The lowest doses of ABT (15 ug/kg) and CGS (30 ug/kg) significantly and selectively reduced responding for nicotine; spontaneous behavior (inactive lever responding) was not altered by these doses. Higher doses of both compounds non-selectively suppressed behavior. During the chronic CGS tests there was no evidence of habituation or desensitization to the effects of the drug as 30 ug/kg selectively suppressed responding for nicotine across all four test sessions. Our findings confirm that directly increasing the activity of A_{2A}Rs (CGS) or increasing the amount of available adenosine (ABT) reduces nicotine self-administration. The findings suggest that the A_{2A}-D_2 heteromer may play a role in nicotine reinforcement and may relate to increased tobacco use in psychiatric disorders with a pathophysiology that includes increased sensitivity of D_2Rs (e.g., psychosis).

Disclosures: S.G. Malone: None. **J.M. Golson:** None. **C.A. Bradley:** None. **R.W. Brown:** None. **C.S. Bailey:** None. **M.I. Palmatier:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.04/OO28

Topic: G.08. Drugs of Abuse and Addiction

Title: Efficacy of a novel selective oral orexin 1 receptor antagonist in rat models of nicotine self administration and reinstatement

Authors: *C. MURRAY[1], G. A. HIGGINS[2], B. P. MARTIN[1], T. NOWAK[1], J. C. FOX[1]
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Abstract: Introduction: The orexin (hypocretin) system in the brain is involved in arousal and wakefulness but also plays a role in behaviours related to addiction and reward, primarily through the Orexin 1 receptor (OX1R). A role for the OX1R in nicotine dependence has been demonstrated in rodent models previously but these studies have predominantly used SB-334867, a tool compound that is only ~ 50 fold selective for OX1R over OX2R and has significant CNS off-target interactions at serotonin and adenosine receptors as well as monoamine and norepinephrine transporters. C4X Discovery has identified C4X_3256, a novel, potent and selective OX1R antagonist, that is being developed as an oral treatment for addictive disorders. **Methods:** Male Sprague Dawley rats were surgically implanted with an intravenous catheter and trained to self administer nicotine on an FR5 schedule. For intravenous self administration (IVSA) studies, rats were randomised into groups once a stable pattern of responding was maintained for at least 2 weeks and were then dosed orally with vehicle, C4X_3256 or varenicline (n=9 per group). Active lever presses and number of infusions were measured in a 1 hour test period using an FR5 schedule after dosing on each of 5 consecutive days. For cue-induced reinstatement studies, following IVSA training in the presence of light and tone cues, rats underwent an extinction period until lever presses were <20% of the rate at the end of the IVSA period. Rats were then randomised into groups (n=12) and dosed with vehicle or C4X_3256 prior to a reinstatement session initiated by light and tone cues in which the number of lever presses over a 1 hour test session was measured. **Results:** A rat receptor occupancy model, measuring displacement of ex vivo radioligand binding to brain tissue following oral dosing of C4X_3256, was used to confirm high levels of compound binding in the brain and define the PK/PD relationship. In the nicotine IVSA model, 30 mg/kg C4X_3256 caused a significant reduction in active lever presses and infusions (IVSA Day 5: Vehicle: 12.9$\pm$2.5 infusions, C4X 30mg/kg: 5.4$\pm$1.7 infusions; $P<0.05$). Pre-treatment with 30 mg/kg C4X_3256 also prevented cue-induced reinstatement of nicotine seeking, as the number of lever presses was not significantly different from the levels during the extinction phase (Day 1: Vehicle: 55$\pm$12 responses, C4X 30mg/kg: 10$\pm$3 responses; $P<0.05$). **Discussion:** The efficacy of C4X_3256 in rat models of nicotine self-administration and cue-induced reinstatement supports development of this compound as a therapy to improve rates of smoking cessation and reduce craving and relapse in smokers who have already quit.

Disclosures: C. Murray: A. Employment/Salary (full or part-time):; C4X Discovery. **G.A. Higgins:** None. **B.P. Martin:** A. Employment/Salary (full or part-time):; C4X Discovery. **T. Nowak:** A. Employment/Salary (full or part-time):; C4X Discovery. **J.C. Fox:** A. Employment/Salary (full or part-time):; C4X Discovery.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.05/OO29

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA Grant AA024674

NIAAA/NIDA Grant AA019682

Title: Extinguishing a compound nicotine+alcohol drug cue and the relative contribution of its individual components

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Abstract: Nicotine and alcohol are two of the most commonly co-abused substances accounting for a significant portion of preventable deaths each year. Furthermore, when nicotine and alcohol are used in combination, rates of several cancers increase significantly. Currently, there are few approved treatments for alcohol or nicotine dependence on their own and none that are approved to treat both. Developing a better understanding of the neurobiology underlying combined nicotine+alcohol use is crucial to ultimately developing better treatments. An important aspect of drug seeking behavior is the various cues, both external/environmental and internal/interoceptive that can drive drug seeking behavior. Considering that these drugs are commonly co-used, their interoceptive effects are frequently experienced together and over time develop into a unique interoceptive cue associated with other reinforcing events. An important question in developing better treatments is whether or not an individual needs to quit both smoking and drinking at the same time to avoid relapse. The current studies assess the effects of extinguishing one or both of the components of a compound nicotine+alcohol (N+A) interoceptive drug cue on reinstatement of goal-tracking behavior. For these experiments, male Long-Evans rats were trained to discriminate a nicotine (0.4 mg/kg) + alcohol (1.0 g/kg) drug state vs water. Rats then underwent extinction sessions in which they received N+A, nicotine alone or alcohol alone. For reinstatement tests, rats were re-exposed to all conditions (N+A, nicotine alone, alcohol alone) with one extinction session between each test. These experiments found that when the N+A compound or nicotine alone was extinguished, reinstatement was blocked upon re-exposure. However, when only alcohol was extinguished, reinstatement was observed upon re-exposure to N+A and to the nicotine component alone. In addition, ongoing work is assessing the role of medial prefrontal cortex and nucleus accumbens core in modulating these behaviors to further unravel the underlying neurobiology. Overall, these findings suggest that nicotine plays an important role in driving this drug-related behavior and that co-users attempting to quit may need

to stop smoking and drinking to be successful. Funding: NIAAA AA024674 (PAR), NIAAA/NIDA AA019682 (JB)

Disclosures: P.A. Randall: None. **J. Besheer:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.06/OO30

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA038843

Title: The effect of flavor conditioned reinforcers and nicotine on extracellular dopamine levels in the nucleus accumbens following nicotine self-administration

Authors: *G. A. DEEHAN, JR[1], A. K. PATTERSON[2], A. SMITH[2], C. A. BRADLEY[2], S. MALONE[2], R. W. BROWN[3], M. I. PALMATIER[2]
[1]Neurosci., [2]Psychology, East Tennessee State Univ., Johnson City, TN; [3]East Tennessee State Univ. Dept. of Biomed. Sci., Johnson City, TN

Abstract: Flavor additives in tobacco products can act as 'conditioned reinforcers' (CRs) - neutral stimuli that acquire reinforcing properties based on an association with primary reinforcers (e.g., sweet tastes). Although nicotine is a weak primary reinforcer, it robustly enhances responding for CRs and the synergistic interactions between nicotine and flavor CRs may promote use and lead to dependence. Drugs of abuse and associated CRs both produce increased extracellular levels of dopamine (DA) in the nucleus accumbens (NAc). The goal of the present study was to determine if the interaction between nicotine and flavor CRs produce alterations in extracellular DA levels in the NAc. To test this hypothesis, male rats were randomly assigned to one of two flavor groups, Unpaired (n=6) or Paired (n=7). Each group received a home-cage flavor-conditioning procedure in which two bottles of solution were placed on the home cage each day, one bottle contained 1% licorice root extract (v/v) and the other contained 0.5% (w/v) grape Kool-Aid. Sucrose (20% w/v) was added to the licorice bottle for the Paired group and to the grape Kool-Aid bottle for the Neutral group. The alternate flavor was unsweetened. Access to the flavored solutions was limited to 40 min per day for 24 days. All rats were instrumented for iv nicotine self-administration. During nicotine self-administration testing two sipper tubes were available in the operant chambers. Licks at both sippers were recorded and meeting the schedule of reinforcement at the 'active' sipper resulted in presentation of 1% licorice (0.12 ml, unsweetened, delivered in the sipper tube) and iv nicotine. Meeting the schedule of reinforcement at the inactive sipper resulted in 0.12 ml of water. Once operant responding was stable (29 sessions), microdialysis probes were implanted into the NAc

approximately 24 hrs prior to testing. Samples were collected at 20 min intervals for approximately 6 h. Following a 90 min washout, the first 3 samples (1h) served as a baseline. The licorice CR was presented alone over the next hour (samples 4-6) and animals received iv nicotine infusions over the third hour (samples 7-9). Samples were collected over two additional hours (10-16) to assess post-nicotine DA levels. There was a trend for increased DA release during presentation of the CR alone in the Paired group, and a trend for reduced DA release in the Unpaired group. During the nicotine administration period and post-treatment samples there was a robust increase in extracellular DA (>200%) only in the Paired group. These findings indicate that the flavor CR robustly enhances DA release in response to nicotine administration.

Disclosures: G.A. Deehan: None. **A.K. Patterson:** None. **A. Smith:** None. **C.A. Bradley:** None. **S. Malone:** None. **R.W. Brown:** None. **M.I. Palmatier:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA040130-01

NIH Grant DA040130-01S1

Title: Blood glucose normalization reduces the enhanced rewarding effects of nicotine in diabetic rats

Authors: *J. IBIAS MARTIN[1], L. E. O'DELL[2], A. NAZARIAN[1]
[1]Pharmaceut. Sci., Western Univ. of Hlth. and Sci., Pomona, CA; [2]Univ. Texas at El Paso, El Paso, TX

Abstract: Diabetes is characterized by compromised processing of insulin (decrease in insulin levels in type 1 and insulin resistance in type 2) that leads to a concomitant increase in blood glucose levels. In turn, diabetes enhances the motivational and rewarding effects of nicotine. In the present study we sought to determine whether the diabetes induced enhancement in nicotine reward is due to direct effects of insulin, or a result of increased glucose levels. Male and female Sprague Dawley rats were treated with streptozotocin (STZ), a pancreatic beta cell toxin, to produce a model of type 1 diabetes or advanced stages of type 2 diabetes. Animals were then placed in a nicotine conditioned place preference (CPP) procedure during which the hyperglycemic state of rats were reduced by means of: a) insulin supplementation, which increases insulin levels and leads to a decrease in blood glucose levels, or b) daily injections of the sodium/glucose cotransporter type 2 (SGLT2) inhibitor dapagliflozin (10 mg/Kg) to decrease

blood glucose levels without altering insulin levels. The results revealed an enhanced preference for the nicotine-paired compartment in the CPP paradigm in STZ-treated male rats, as compared to non-diabetic control rats. Insulin supplementation or dapagliflozin administration normalized the enhanced nicotine CPP in STZ-treated rats. STZ-treated female rats did not exhibit the enhanced preference for the nicotine-paired compartment observed in male rats. In general, CPP scores for female rats were lower than for male rats at the dose of nicotine used in this study. These results suggest that hyperglycemia, rather than direct effects of insulin are responsible for the enhanced rewarding effects of nicotine found in diabetic rats.

Disclosures: J. Ibias martin: None. **L.E. O'Dell:** None. **A. Nazarian:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.08/OO32

Topic: G.08. Drugs of Abuse and Addiction

Support: Virginia Youth Tobacco Programs (VCU)

Virginia Foundation for Healthy Youth

Title: Age-related changes in nicotine consumption and social interactions in adolescent mice

Authors: J. KO, R. L. MURPHY, B. N. MARTIN, *K. J. FRYXELL
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Abstract: We previously reported that social isolation (vs. pair housing) of adolescent mice dramatically increased the amount of nicotine solution consumed (as a percent of total fluid volume) during an extended test of voluntary oral nicotine consumption. This increased nicotine consumption was particularly evident in adolescent males, from the first period of nicotine access in early adolescence (postnatal day 30 (p30)), to the end of this 28-day experiment, which was in late adolescence (p58). Here we extend this paradigm to mice who were exposed to nicotine starting on p40 (mid adolescence) and continuing until p68 (young adulthood). The experimental design in the current report was similar to our previous report: mice were given unlimited access to two water bottles, one containing water and the other containing a nicotine solution, and their nicotine consumption was measured (as a percent of total fluid consumed) over a 28-day time period. Overall, the mice who began in mid adolescence (p40) consumed significantly more nicotine than the mice who began in early adolescence (p30). We also found that adolescent males whose nicotine consumption began on p40 showed a significant social effect (single-housed males drank more nicotine than pair-housed males), but the magnitude of the social effect was reduced, in comparison to adolescent males whose consumption began on

p30. Adolescent females whose nicotine consumption started at p40 showed no social effect, but females whose nicotine consumption started on p30 showed a small (but significant) social effect. In both sexes, the social effect was significantly greater when nicotine consumption began during early adolescence. These data were analyzed by univariate ANOVA, which revealed significant main effects of Sex ($p < 0.05$) and Age ($p = 0.001$). We also found a highly significant interaction of Housing x Age ($p < 0.005$), where the "Housing" parameter represented whether the mice had been single-housed or pair-housed during nicotine consumption. Taken together, these results show that the relative importance of social reward (in influencing nicotine consumption) declines with age during adolescence, in part because the strength of nicotine dependence also appears to increase with age during adolescence.

Disclosures: J. Ko: None. **R.L. Murphy:** None. **B.N. Martin:** None. **K.J. Fryxell:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA grant DA11064

NIDA grant DA034097

NIDA grant DA036569

Title: Analysis of economic demand for nicotine using an abbreviated behavioral economics protocol in rats

Authors: *J. A. MARUSICH[1], G. L. POWELL[2], J. S. BECKMANN[4], J. L. NEISEWANDER[3], A. P. DEL FRANCO[2], J. GOENAGA[2], C. D. GIPSON[2]
[1]Ctr. for Drug Discovery, RTI Intl., Research Triangle Park, NC; [2]Psychology, [3]Sch. of Life Sci., Arizona State Univ., Tempe, AZ; [4]Univ. of Kentucky, Lexington, KY

Abstract: The United States FDA regulates the nicotine content of cigarettes as a potential mechanism to reduce nicotine and tobacco consumption. Considerable research is devoted to understanding how tobacco product taxation could influence human consumption of nicotine. Recent research has employed behavioral economics principles to analyze consumption of many drugs of abuse, and determine values for drug demand and sensitivity to the cost-benefit ratio across multiple doses. Most past research has used drug self-administration with progressive decreases in dose over many days or weeks. In the present study, a behavioral economic analysis was used to investigate the validity of an abbreviated dose reduction protocol. Rats were trained to self-administer nicotine. Once responding was established, rats began dose reduction protocols

either across consecutive days or within one session. Light and tone stimuli paired with infusions were proportionally reduced, and then sessions were conducted without cues. Behavior economics were analyzed with an exponential demand equation. Within-session dose reduction produced the same shape curve as daily dose reduction; however, daily dose reduction produced greater nicotine consumption than within-session reduction. Cue removal produced steeper curves, indicating a decrease in reinforcing strength of nicotine compared to infusions paired with cues. Results illustrate that an abbreviated dose-response protocol paired with altered stimulus cues captures the typical behavioral economic features of a multi-day dose-response protocol in one session, and thus allows for more efficient analysis of nicotine demand. This abbreviated protocol provides a model for testing multiple doses or multiple drugs of abuse, and for examining other experimental manipulations commonly employed during within-session analysis. Future research will further validate the abbreviated nicotine dose-response protocol using other techniques commonly employed in behavioral neuroscience research, such as environmental enrichment, manipulation of neural circuitry underlying nicotine addiction via Designer Receptors Exclusively Activated by Designer Drugs, and pharmacotherapeutic treatment.

Disclosures: J.A. Marusich: None. **G.L. Powell:** None. **J.S. Beckmann:** None. **J.L. Neisewander:** None. **A.P. Del Franco:** None. **J. Goenaga:** None. **C.D. Gipson:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01-DA021274

NIH Grant R25-DA033613

Title: Sex differences and the role of ovarian hormones in nicotine withdrawal in rats

Authors: *R. J. FLORES GARCIA, K. P. URIBE, B. CRUZ, V. CORREA, L. M. CARCOBA, A. LOPEZ, L. E. O'DELL
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Abstract: Introduction: Clinical reports indicate that negative affective states elicited during smoking abstinence are more intense in women than men, and the intensity of the withdrawal syndrome fluctuates across the estrous cycle. The goal of the present study was to characterize sex differences and the role of ovarian hormones in physical signs and negative affective states produced by nicotine withdrawal in female, ovariectomized (OVX) female and male rats. We

also assessed whether the magnitude of the behavioral effects of nicotine withdrawal fluctuates across the 4-day estrous cycle in female rats. **Methods:** Female rats first received either a surgical sham or an ovariectomy procedure. Fifteen days later, all female and male rats were implanted with an osmotic pump that delivered nicotine for 14 days. On the test day, separate groups received an injection of vehicle or the non-selective nicotinic receptor antagonist, mecamylamine (1.5 or 3.0 mg/kg) to precipitate withdrawal. Rats were then tested in a series of behavioral tests that included the physical signs of withdrawal and two tests of anxiety-like behavior (elevated plus maze and light/dark transfer). Immediately after testing, trunk blood was collected and blood plasma was analyzed using ELISA procedures for the stress hormone, corticosterone and the gonadal hormones, testosterone and progesterone. Female rats received vaginal lavage procedures to verify the phase of the estrous cycle on the test day. **Results:** Our results revealed that females displayed a larger magnitude of physical signs and anxiety-like behavior during withdrawal as compared to males and OVX female rats. Also, the females that were tested during estrus displayed the highest magnitude of physical signs of withdrawal. The intact females also displayed the highest increases in corticosterone levels during withdrawal. Although the males did show physical signs of withdrawal, this effect was not correlated with testosterone levels. **Discussion:** Our results provide evidence for a relationship between stress and ovarian hormones, and the expression of nicotine withdrawal in females.

Disclosures: R.J. Flores Garcia: None. **K.P. Uribe:** None. **B. Cruz:** None. **V. Correa:** None. **L.M. Carcoba:** None. **A. Lopez:** None. **L.E. O'Dell:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 079.11/OO35

Topic: G.08. Drugs of Abuse and Addiction

Support: The CSTP at Virginia Commonwealth University

Title: Effect of menthol additive on nicotine intake and relapse vulnerability in a rat model of adolescent-onset nicotine addiction

Authors: *T. NESIL, S. NARMEEN, W. J. LYNCH
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Abstract: Population data in humans suggest that menthol may increase vulnerability to cigarette/nicotine use and relapse; however, it is not yet known whether such effects are caused by these menthol products or inherent to the populations using them. The goals of this project were to determine in a rat model the effect of menthol additive on nicotine self-administration and relapse vulnerability focusing on the potential for pharmacological interactions of menthol

and nicotine. To do so, menthol was added directly to the intravenous nicotine solutions (0.01 mg/kg/infusion), which allowed us to eliminate potential sensory cue effects. A low, moderate, and high dose of menthol (0.17, 0.34, and 0.68 mg/kg/infusion) were tested to approximate exposure levels in human smokers. Given an apparent vulnerability in human adolescents to menthol cigarette use, we used an adolescent-onset model, and to capture human smoking conditions, we used an extended access paradigm that allowed 23-hr/day access to nicotine. Once rats acquired nicotine self-administration, they were randomly assigned to one of five groups (nicotine alone), nicotine + low menthol, nicotine + moderate menthol, nicotine + high menthol, or menthol alone (0.17-0.68 mg/kg). Rats were given unrestricted access to drug infusions for 23-hrs/day for a total of 10 days. Drug seeking was assessed under an extinction/cue-induced reinstatement procedure following a 10-day abstinence period. Each of groups that self-administered nicotine (alone or in combination with menthol) self-administered significantly more infusions than the menthol alone group; however, no other group differences were observed for intake. Each of the groups that self-administered nicotine (alone or in combination with menthol) also responded at higher levels under extinction and reinstatement testing conditions as compared to the menthol alone group. Significant group differences were also observed between the nicotine alone and the nicotine plus menthol groups for extinction and reinstatement responding. However, in contrast to data in humans, menthol decreased subsequent extinction responding, particularly at the low dose, and dose-dependently decreased subsequent reinstatement responding. These findings are surprising, and suggest that under conditions that mimic human nicotine addiction, pharmacological interactions of menthol and nicotine reduce, rather than increase, relapse vulnerability. Future research is needed, however, to determine whether these pharmacological interactions can be negated, and potentially reversed via sensory cue effects, as would be expected based on the epidemiological findings.

Disclosures: T. Nesil: None. **S. Narmeen:** None. **W.J. Lynch:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

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Program#/Poster#: 079.12/OO36

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA038843

Title: Flavor conditioned reinforcers promote dependence-like behavior in rats self-administering nicotine

Authors: *A. SMITH[1], C. A. BRADLEY[2], A. K. PATTERSON[2], E. SANDERS[2], J. M. GOLSON[3], C. S. BAILEY[2], S. G. MALONE[3], M. I. PALMATIER[2]

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Abstract: Flavor additives in tobacco products are 'conditioned reinforcers' (CRs) - neutral stimuli that acquire reinforcing properties based on an association with primary reinforcers (e.g., sweet tastes). Although nicotine is a weak primary reinforcer, it robustly enhances responding for CRs and the synergistic interactions between nicotine and flavor CRs may promote use and dependence. The goal of the present study was to determine if the interaction between nicotine and flavor CRs could promote dependence-like behavior (responding for the drug in the face of negative consequences). To test this hypothesis, intravenous (iv) nicotine self-administration with an oral licorice flavor was challenged in a conflict procedure - escalating concentrations of quinine hydrochloride were added to the oral solution. Male rats were randomly assigned to one of two flavor groups, Neutral (n=15) or CR (n=16). Each group received a home-cage flavor-conditioning procedure in which two bottles of solution were placed on the home cage each day, one bottle contained 1% licorice root extract (v/v) and the other contained 0.5% (w/v) grape Kool-Aid. Sucrose (20% w/v) was added to the licorice bottle for the CR group and to the grape Kool-Aid bottle for the Neutral group. The alternate flavor was unsweetened. Access to the flavored solutions was limited to 40 min per day for 24 days. All rats were instrumented for iv self-administration and randomly assigned to receive 20 or 40 ug/kg unit nicotine doses (n=7-8 per dose per group). During nicotine self-administration testing two sipper tubes were available in the operant chambers. Licks at both sippers were recorded by the computer; meeting the schedule of reinforcement at the 'active' sipper resulted in presentation of 1% licorice (0.12 ml, unsweetened, delivered in the sipper tube) and iv nicotine. Meeting the schedule of reinforcement at the inactive sipper resulted in 0.12 ml of water. Once operant responding was stable (14 sessions), quinine hydrochloride was added to the licorice in increasing concentrations (0.1, 0.3, and 1 mM). Rats self-administered more of the 20 ug/kg dose than the 40 ug/kg dose, but flavor status (Neutral vs. CR) did not alter acquisition. At the 20 ug/kg unit dose quinine robustly reduced nicotine intake for both Flavor-Neutral and Flavor-CR groups. However, at the 40 ug/kg dose quinine only reduced nicotine intake for the Flavor-Neutral group, and not significantly reduce intake in the Flavor-CR group. These findings indicate the the interaction between nicotine and flavor CRs can result in dependence-like behavior when the CRs are self-administered with moderate to high unit nicotine doses.

Disclosures: A. Smith: None. **C.A. Bradley:** None. **A.K. Patterson:** None. **E. Sanders:** None. **J.M. Golson:** None. **C.S. Bailey:** None. **S.G. Malone:** None. **M.I. Palmatier:** None.

Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

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Startup funds from the VCU School of Pharmacy

Title: Oleoyl glycine produced by brain trauma reduces nicotine reward and withdrawal in mice

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Abstract: Cigarette smokers presenting with traumatic brain injury (TBI)-induced damage of the insula cortex display cessation of nicotine addiction. Furthermore, preclinical data implicate the insula in control processes that moderate addictive behavior. These observations combined suggest that a neurochemical within the insula cortex that is sensitive to brain injury might counteract the rewarding effects and dependence liability of nicotine. In order to identify the existence of this hypothesized neurochemical, we tested whether experimental TBI in mice would lead to the elevation of an endogenous anti-addiction mediator within the insula. Using targeted lipidomics techniques based on LC-MS and LC-MS/MS, among several investigated lipids, which included endocannabinoids, N-acylethanolamines, N-acyldopamines, N-acylserines and N-acylglycines, experimental brain injury elicited a profound increase of a largely uncharacterized member of the latter class, N-oleoyl glycine (OlGly) in insula cortex, but not in comparison brain regions (i.e., hippocampus and cerebellum). These findings prompted us to test whether exogenous administration of OlGly would alter nicotine reward, as assessed in the conditioned place preference (CPP) paradigm, as well as precipitated withdrawal behaviors in nicotine-dependent mice. Interestingly, we found that OlGly reduced both nicotine CPP and withdrawal responses. Because the endogenous cannabinoid system modulates the reinforcing effects of nicotine, we conducted a series of in vitro (i.e., radioligand binding in CB1 or CB2 receptor transfected HEK-293 cells) and in vivo (i.e., common pharmacological cannabimimetic

effects in the presence or absence of the high efficacy CB1/CB2 receptor agonist CP55,9940) studies to test whether this system mediates the “anti-reward” effects of OlGly. The results did not show evidence of the involvement of this system in the “anti-reward” effects of OlGly. Considering that OlGly has a chemical structure similar to N-palmitoylethanolamide, which acts as an endogenous PPAR-α ligand, we examined the potential involvement of this target in complementary in vitro and in vivo studies. OlGly not only behaved as a PPAR-α receptor agonist in a functional activity luciferase assay, but also the PPAR-α receptor antagonist GW6471 prevented the “anti-reward” effects of OlGly in nicotine CPP. These findings contribute to the growing interest in the physiological relevance of long chain fatty acid amides by identifying OlGly as an endogenous PPAR-α receptor agonist and potential endogenous “anti-nicotine addiction” molecule.

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Poster

079. Nicotine: Reinforcement, Seeking, and Reinstatement

Location: Halls A-C

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Program#/Poster#: 079.14/PP2

Topic: G.08. Drugs of Abuse and Addiction

Title: Beta-2 nAChRs on DA and GABA VTA neurons respectively signal the aversive and rewarding conditioned motivational effects of acute nicotine

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Abstract: The ventral tegmental area (VTA) of the mesolimbic dopamine system, containing both dopamine (DA) and gamma-aminobutyric acid (GABA) neurons, has been implicated in the processing of nicotine's acute motivational effects. Our previous work showed that nicotine injected directly in to the VTA in previously drug-naive animals produces a DA-mediated aversive response as well as a GABA-mediated rewarding motivational response. The β2 subunit of the nicotinic acetylcholine receptor (nAChR) is necessary and sufficient for nicotine motivation, and can be found of both DA and GABA neurons in the VTA. We hypothesized that β2 nAChRs on VTA DA neurons mediate acute nicotine aversions while β2 nAChRs on VTA GABA neurons mediate acute nicotine reward. We selectively re-expressed the β2 nAChR subunit on GABA or DA neurons in the VTA of β2 knockout (KO) mice and subjected these mice and their controls to place conditioning after injection of a low (0.35 mg/kg) or high (1.75 mg/kg) dose of acute nicotine. Our results show that WT mice will find the low dose of nicotine non-motivational and will show an aversive motivational response to the high dose of acute nicotine, while global β2 KO mice will not show a preference or aversion to either dose. Selective re-expression of the β2 nAChR on VTA DA neurons rescued the aversive but not a rewarding motivational response to acute nicotine, while re-expression of the β2 nAChR on VTA GABA neurons made the non-motivational low dose of acute nicotine rewarding but did not rescue the aversive motivational response to the high dose. These results doubly dissociate the role of DA and GABA VTA neurons in the aversive and rewarding motivational responses, respectively, to acute nicotine.

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Poster

080. Working Memory: How Memory Works

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

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University of Florida University Scholar Award to MMB

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Title: Brain aging is associated with regional and isoform-specific reductions to glutamic acid decarboxylase

Authors: J. M. MOATS[1], J. A. MCQUAIL[2], M. M. BRUNER[2], C. BANUELOS[3], D. A. SCHEUER[4], *J. L. BIZON[2]
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Abstract: Gamma-aminobutyric acid (GABA) is the brain's chief inhibitory neurotransmitter and changes to inhibitory signaling across the lifespan may be an underlying cause of memory disorders across psychiatric and neurodegenerative conditions. The septohippocampal system, including the medial septum/vertical diagonal band (MS/VDB) and the hippocampus (HPC), is susceptible to aging and neurodegenerative disease as well as a target for the actions of stress hormones that can contribute to impaired memory. While much work to date has examined the status of cholinergic neurons and synapses in this system, relatively few studies have considered changes to GABAergic elements of this network. We hypothesized that the levels of GABA-synthesizing enzymes in MS/VDB and HPC are sensitive to change with age and co-vary with cognitive status. In Experiment 1, we measured GAD isoforms in homogenates prepared from MS/VDB and HPC harvested from young adult (6 months) and aged (22 months) rats that were previously characterized for memory performance on a spatial learning task. GAD-67 was significantly reduced in the HPC of aged rats compared to young but GAD-65 was unchanged. In the MS/VDB, neither GAD-65 nor GAD-67 changed with age, but a planned comparison revealed a selective reduction of GAD-67 only in aged rats with impaired spatial learning. Experiment 2 utilized a chronic variable stress paradigm to determine whether experimentally induced dysfunction of hypothalamic-pituitary-adrenal (HPA) axis in young adult rats is sufficient to mimic age-related reduction of HPC GAD-67. After 14 days of twice-daily exposure to an unpredictable schedule of various psychogenic stressors including predator urine, forced swims, cage-switch and restraint, HPC was collected from stressed rats and appropriate unstressed controls and GAD isoforms were measured as in Experiment 1. Unexpectedly, levels of GAD-65 and GAD-67 were unchanged by exposure to the stress paradigm. In summary, aging is associated with a selective reduction in the level of GAD-67 in the HPC and in the MS/VDB of memory-impaired rats. The basis for this decline is unknown, but our work suggests stress/HPA dysfunction is not the mediator of this phenomenon. Furthermore, preserved level of GAD-65 in the aged brain could compensate for reduced GAD-67 to maintain synaptic GABA availability. Future work will examine other markers of GABA signaling in the context of aging and stress to fully characterize dysregulation of inhibitory neurotransmission in these two physiological states.

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Poster

080. Working Memory: How Memory Works

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Support: AG047266

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McKnight Brain Research Foundation

1R01AG049722

Title: Connectivity changes after cognitive training in young and aged rats

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Abstract: Changes in large-scale neural connectivity are a hallmark of brain aging that have been linked to cognitive decline. Recent behavioral models for probing the integrity of inter-regional communication along with advances in functional MRI offer a unique opportunity to study functional connectivity in conjunction with quantification of the neurobiological mechanisms that underlie alterations in large-scale network communication. In this study, we determined how cognitive training on an object-place paired association (OPPA) task, which requires interactions between prefrontal, medial temporal and subcortical structures, altered functional connectivity in young (4 mo, n = 5) and aged (24 mo, n = 5) Fischer 344 x Brown Norway F1 hybrid rats. A resting state fMRI dataset was collected in a 11.1 Tesla Bruker system. All rats were scanned for three sessions: before cognitive training, after two weeks of training on the OPPA task in which both young and aged rats were not performing above an 80% criterion (second session), and after four weeks of OPPA training in which the young rats, but not old, were performing at criterion (third session). A 1-shot spin echo EPI sequence was acquired with acquisition parameters for a total acquisition time of 10 mins (an image was acquired every 2s). Anatomical scans for image overlay and reference-to-atlas registration were collected using a fast spin echo sequence. Time series fMRI signals were extracted from each region of interest (ROI) based on the atlas-guided seed location (150 total areas). The correlation values of the graphs were thresholded for each subject to create matrices with equal densities (e.g the top 15% correlation values). Network matrices were normalized by the highest correlation value, such that all matrices had edge weight values ranging from 0 to 1. The networks were quantified with the following graph theory metrics: *node strength* (sum of edge weights), and rich club (highly

interconnected subnetwork commonly termed as hubs). Young rats did not show differences in global node strengths between the three sessions; however, the aged rats showed an increased in node strength connectivity after the first training session at high node strength values. The areas involved in increasing the node strength values in the aged group were: anterior cingulate, cortical, striatal. Particularly the rich club increased after the first session in the aged group and was maintained during the third session. This suggests an engagement in learning as rats aged in a subnetwork (comprised of anterior cingulate, striatal area, somatosensory, motor, insular, and motor cortex areas) that is not engaged in learning of young rodents.

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Poster

080. Working Memory: How Memory Works

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Title: Age-related changes in the perirhinal-hippocampal-prefrontal cortical circuit: evidence for neural compensation in aged rats

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Abstract: The increase in the average lifespan has not been met with a commensurate improvement in cognitive healthspan. In fact, loss of cognitive function and declining neuronal metabolism are hallmarks of advanced age, and little is understood regarding how changes in neuronal signaling affect behavioral output. Moreover, there is considerable variability in the behavioral phenotypes of old humans and animals. Critically, it is not known whether neural systems in the aged brain reorganize in cognitively intact older animals, showing evidence of compensation, or conversely if these systems maintain function into advanced age. The aim of the present study was to determine the extent to which brain activation patterns during a bi-conditional association task (BAT), which is sensitive to detecting age-related impairments and

requires interactions between the prefrontal cortex (PFC), perirhinal cortex (PER), and hippocampus (HPC), differ between young and aged rats. Importantly, all rats were trained to perform similarly in order to examine the extent to which activation patterns across the PFC, PER and HPC reorganize in old age when behavioral output is comparable. Cellular activity during BAT and a control task was measured by quantifying the number of cells expressing the immediate early gene, *Arc*. *Arc* transcription is initiated by patterned neuron spiking associated with behavior. Because *Arc* is an effector protein that is translocated to the cytoplasm ~20 min after cell activity, we can determine the neural ensembles activated at two distinct time points based on the cellular location of *Arc* mRNA. The results indicated that there was a significant main effect of task ($p < 0.02$) for all regions examined, as well as an age by region interaction ($p < 0.05$), suggesting that age did not impact all regions similarly. In fact, aged rats showed elevated activity, compared to young animals, in the PFC during both tasks. In contrast, all rats had elevated activity in CA1 (HPC) during the BAT as compared to the control walking task. In the PER there was decreased activity in aged rats compared to young rats across both tasks. Together, these data suggest that anterior regions may be compensating for a decrease in function in the PER. The observation that neural activity patterns differ between young and old animals, even when their behavioral performance is comparable, supports the idea that neural networks in the aged brain may reorganize to optimize behavioral output as one region becomes dysfunctional. Future studies will incorporate retrograde tracing with *Arc* imaging to investigate signaling across these regions with anatomical specificity.

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Poster

080. Working Memory: How Memory Works

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Title: Optogenetic inactivation of basolateral amygdala in young rats recapitulates aged rats' ability to delay gratification in an intertemporal choice task

Authors: *C. M. HERNANDEZ, III[1,4], C. A. ORSINI[2,4], C. LABISTE[1], S. M. SINGHAL[3], S. N. BURKE[1,4], C. J. FRAZIER[3], B. SETLOW[2,4], J. L. BIZON[1,4]
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Abstract: Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. Such decisions require integration of existing reward representations (based on prior experience) with valuation of the organism's current wants and needs (incentive motivation). Prior studies in both humans and rodents show that relative to young adults, aged subjects are better able to delay gratification, and generally prefer large, delayed over small, immediate rewards. While the neural circuit and molecular changes that mediate these age differences in intertemporal choice are unknown, lesion studies consistently implicate the basolateral amygdala (BLA) in motivation and affective decision making. The current experiments first used optogenetic approaches to determine the effects on choice behavior of temporally discrete BLA inactivation during an intertemporal choice task. Young adult (6 mo., n=8) Fischer 344 x Brown Norway F1 hybrid (FBN) rats were surgically implanted with cannulae targeting BLA, into which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was delivered, and optic fibers were cemented. Rats were subsequently trained on an adjustable delay, intertemporal choice task in which preference for small vs. large rewards was evaluated in presence of increasing delays to large rewards. Upon reaching stable baseline performance, light-induced BLA inactivation was performed during the trial epoch in which rats deliberate between large, delayed and small, immediate reward options. To control for effects of repeated laser stimulation on choice behavior, in other sessions, rats received discrete light-induced inactivation only during intertrial intervals (ITIs). In comparison to both baseline and ITI inactivation, discrete BLA inactivation during deliberation significantly biased rats towards choice of the large, delayed reward, and produced a pattern of choice performance that mimics that of aged rats. In a second cohort of behaviorally naïve young and aged FBN rats, total RNA was extracted from the BLA and low-density RT-qPCR plates were used to assess basal expression of genes involved in excitatory glutamatergic and inhibitory GABAergic signaling. Broadly, transcripts associated with glutamatergic signaling were reduced in the aged BLA, suggesting this brain region undergoes molecular changes in aging that render it hypoactive. Together, these findings suggest that age-associated shifts in BLA excitatory/inhibitory signaling dynamics attenuate the influence of incentive motivation on cost-benefit decision making, and contribute to the enhanced ability of older subjects to delay gratification.

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Poster

080. Working Memory: How Memory Works

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Topic: H.01. Animal Cognition and Behavior

Support: NIMH 1R01MH109548-01A1

NIA R01AG055544

Title: A wave-turbulence description of activity flow in the hippocampus

Authors: *A. SHEREMET[1], A. P. MAURER[2]
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Abstract: The complicated, multi-scale architecture of the brain is a formidable obstacle in modeling brain activity, and ultimately, understanding the dynamics of cognitive behavior. While some brain components exhibit a clear hierarchy of directed activity-flow loops (Felleman and Van Essen, 1991), in others, the specificity of projections are approximate at best, and recurrent projections may be so dense that a local region may resemble an isotropic medium. These structures can be described as isotropic and homogeneous 2-dimensional random neural lattices. The typical scale of these regions is typically mesoscopic (Freeman, 1998), much larger than the microscopic neuron scale and much smaller than the macroscopic scale of the global brain. We shall refer to these regions of random neural lattices as "neuron pools".
Observations suggest that brain activity in neuron pools can be characterized as stochastic and weakly nonlinear. Stochasticity is reflected in the LFP trace randomness, which in turn expresses the non-local character of the activity, the mass action (Freeman, 1998). In a homogeneous and isotropic neuron pools, this suggests that "information" is carried by propagating "waves" whose physical support are neuron assemblies of various scales. The nonlinear character of the LFP trace reflects the weak interaction (i.e., transfer of energy and phase correlations) within the spectrum of neural-assembly scales.
We propose to study the collective dynamics of neurons in the mesoscopic pools using the wave turbulence description (Kolmogorov, 1941; Zakharov, 1961; Nazarenko, 2011). The wave turbulence approach (WT) was developed for studying the kinetics (statistical physics) of systems with a large number of components that interact weakly. The WT approach generates universal equations for the nonlinear evolution of moments (cummulants) of the statistics of the system. The mesoscopic, stochastic and weakly nonlinear character of neuron pools fit the standard WT description. In fact, techniques used for the nonlinear analysis of LFPs (Sheremet et al., 2016), have specific meanings in this formalism. One of the most significant successes of the

WT approach was the prediction of self-similar states with power-law spectral shapes, the Kolmogorov-Zakharov spectra.

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Poster

080. Working Memory: How Memory Works

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Title: Impact of age- and stress-related neuroendocrine dysfunction on working memory and GABAergic synaptic markers in prefrontal cortex

Authors: *J. A. MCQUAIL[1], S. GHAY[1], M. M. BRUNER[1], E. G. KRAUSE[2], B. SETLOW[3], D. A. SCHEUER[4], J. L. BIZON[1]
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Abstract: Normal aging is associated with impaired cognition, including working memory supported by the prefrontal cortex (PFC). Our prior work strongly implicates altered PFC glutamatergic and GABAergic signaling in age-related working memory impairment. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis also accompanies the aging process and it has been proposed that the cumulative effects of stress and concomitant glucocorticoid exposure over the lifespan exacerbate neural changes that mediate the emergence of cognitive deficits. As the PFC is enriched in glucocorticoid receptors, the present study tested the hypothesis that age-related differences in HPA function associate with working memory ability and that chronic stress recapitulates adverse effects of aging on working memory and PFC glutamatergic/GABAergic signaling protein expression. First, we evaluated the relationship between working memory and circulating corticosterone (CORT) in aged rats. Young adult (4-6 mo) and aged (22-24 mo) rats were characterized for working memory ability using a delayed response task. As in our previous work, working memory in aged rats was less accurate than

young, although aged performance spanned a broad range with some aged rats performing similar to young (unimpaired) and others performing worse than young (impaired). Basal CORT measured across the diurnal cycle was greater in aged rats than in young but this elevation was not associated with working memory. When challenged with a stressor (1 h restraint), stress-induced CORT was positively correlated with working memory performance of aged rats. Next, we determined the extent to which chronic variable stress can recapitulate the behavioral and molecular consequences of advanced aging. Young adult rats were exposed to a 21-day randomized schedule of twice-daily stressors including forced swims, water in cage, restraint stress and exposure to predator urine. Accuracy of working memory declined over the course of the regimen in chronically stressed rats compared to non-stressed controls. On the 22nd day, rats were sacrificed and PFCs dissected for molecular analysis. While markers affiliated with excitatory signaling (NMDARs, VGluT1) were not reliably changed by stress, expression of GABA(B)R1a, a presynaptic GABA autoreceptor, and VGAT, the presynaptic vesicular GABA transporter, were significantly reduced in the PFC of stressed rats. Collectively, our findings identify a causal role for stress in PFC GABA signaling alterations that could contribute to impaired working memory.

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Poster

080. Working Memory: How Memory Works

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Support: R01 MH 109548

McKnight Brain Research Foundation

Title: Spectral evolution of the medial entorhinal local-field potential across behavior

Authors: ***J. KENNEDY**[1], Y. QIN[2], J.-M. MIZELL[3], C. ELVIRA MARTIN[3], D. T. GUENTHER[4], C. HERDEGEN[5], S. N. BURKE[3], A. SHEREMET[6], A. P. MAURER[5]
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Abstract: Higher cognitive functions require the large-scale integration of the activity of single neurons. Connecting the large scale with the small scale, however, necessitates an understanding of activity at the “mesoscopic scale”. Theoretically, large-scale organization is entrained by the

higher amplitude, slower frequency theta rhythms, while more local organization of cooperating neurons occurs in the gamma range. Support of this hypothesis comes from research demonstrating that neurons in layer II and III of the entorhinal cortex discharge in temporally defined “gamma windows” (Chrobak & Buzsaki, 1998). Moreover, an animal model of schizophrenia, associated with a reduction in parvalbumin positive interneurons, exhibit a decrease in gamma power in layer II of the medial entorhinal cortex (Cunningham et al., 2006). Therefore, combined with a wealth of other evidence, oscillatory coordination appears to be functional as well as a site of disruption in mental health disorders. Therefore, we sought to define the spectral evolution of the local-field potential (LFP) in the medial entorhinal cortex of rats across a variety of behaviors including sleep, novelty and learning. The investigation of spectral evolution across circumstances in which firing rates of neurons are known to change provides a physical description cortical function. Importantly, this forms the basis of a mechanistic description of how neurons act in concert in the support of adaptive behaviors.

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Poster

080. Working Memory: How Memory Works

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Title: Untangling the cortical-hippocampal circuitry of spatial delay discounting

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MAURER[1]
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Abstract: Decisions are often made in the face of dynamic contingencies, which requires optimization via updating of cost vs. reward representations. Given the complexity of these operations, decision-making requires orchestrated communication across brain regions, including the medial temporal lobe and frontal cortices. Despite this multiregional dependency, research on the relative contributions of frontal cortical regions (FC) to value representation and the hippocampus (HPC) to predictive processing has largely continued independently (Wikenheiser & Schoenbaum, 2016). Although FC regions receive a direct projection from the ventral hippocampus, reciprocal connections from FC to both dorsal and ventral HPC are indirect. Regions that are most likely to relay information between FC and HPC are the lateral entorhinal cortex (LEC) and the thalamic nucleus reuniens (Vertes, 2006). The current experiments investigated whether inactivation of nodes in the FC-HPC circuit influence behavior on a dynamic decision-making task that requires updating of outcome representations throughout. Young adult male F344 x Brown Norway hybrid rats were trained on a spatial delay discounting task, which tests preference for a large reward preceded by a dynamically changing delay vs. a small immediate reward. The dynamic delay increases each time the rats choose the large reward side and decreases each time they choose the small reward side. This allows the rats to titrate the dynamic delay on the large reward side to their preference, then alternate between the two sides to keep the delay stable. After behavioral characterization, rats were implanted with cannulae targeting the orbitofrontal cortex (OFC) and dorsal HPC, or the LEC. We found that inactivation of dorsal HPC or OFC led to dissociable impairments: HPC inactivation caused increased preference for the small reward and increased deliberation times, while OFC inactivation caused increased preference for large rewards and decreased deliberation times. Furthermore, disconnection of dorsal HPC and OFC by inactivating contralateral hemispheres prevented rats from optimizing a stable delay duration, meaning that they did not alternate to stabilize the delay and instead continually altered the delay. Notably, the behavioral effect of HPC-OFC circuit disruption was distinct from effects of inactivating HPC or OFC independently. Behavioral effects of LEC inactivation were similar to those resulting from HPC-OFC circuit disruption. Together, these results suggest that coordinated activity across the FC-MTL circuit is crucial for deriving an optimal set point in spatial delay-discounting.

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Poster

080. Working Memory: How Memory Works

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 080.09/PP11

Topic: H.01. Animal Cognition and Behavior

Support: R01 MH 109548

McKnight Brain Research Foundation

Title: Network metrics identify critical role of interneurons in neural circuits and bilateral synchronization of CA1

Authors: *C. HERDEGEN[1], N. DELROCCO[1], J.-M. MIZELL[1], K. DIBA[3], R. VACCA[2], A. P. MAURER[1]
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Abstract: Structure and function have a dynamic interplay in the brain, organizing the flow of activity in support of behavior. While this observation has placed neural dynamics in the spotlight, it has been difficult to quantify changes in functional connectivity across a network of neurons. To address this gap in knowledge, we applied metrics from graph theory on networks of activity synchronization between neurons to identify the key roles of interneurons in neural circuits, as well as the effects of behavioral state on neural communication. The synchronization networks were constructed from bilateral recordings of populations of CA1 neurons in four rats, made immediately before, during, and after the rats explored a novel maze (data generously provided by A. Grosmark, J. Long and G. Buzsáki). Neurons were treated as network nodes and directed edges were constructed from millisecond timescale interactions detected between in cell pairs (Diba et al., 2014). Interneurons displayed a high bridging centrality and degree in the networks, indicating their role as hubs and “key players”. We observed a central core of synchronous interneurons in all epochs, suggesting they function as both the skeleton and the clock for neural circuits (Buzsáki and Chrobak, 1995). As rats were introduced to the novel maze, modularity of the hemisphere partition decreased significantly, indicating higher cohesion and greater synchronization between hemispheres during learning, which was facilitated by interneuronal pathways. The networks also exhibited scale-free characteristics that tend to optimize speed and efficiency of communication, similar to those seen in other systems such as social networks, maps of connected proteins, and the internet.

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Poster

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McKnight Brain Research Foundation

Title: Propagation and spectrum evolution of local-field potential within single lamina of neurons

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Abstract: The anatomy of the telencephalon is characterized by local laminar organizations that contain a rich variety of neuronal types. For example, rodent hippocampal CA1 has a highly conserved anatomical organization consisting of ~85% excitatory principal neurons and ~15% inhibitory interneurons (Freund & Buzsáki 1996; Amaral & Witter 1989). Similarly, mammalian neocortex is a six-layered structure mainly comprised of projection pyramidal cells and short axon interneurons (Defelipe et al., 2002). As anatomy provides the inherent framework within which neural activity can flow, but with dynamics that can change on the millisecond timescale, we investigated the parameters that give rise to propagating activity patterns using anatomically and biophysically relevant neurons (Ermentrout & Kleinfeld, 2001). A stochastic synaptic connection distribution model was applied to assess neural activation wave propagation, as well as the local-field potential (LFP) within a lamina composed of excitatory pyramidal neurons and inhibitory interneurons. These data form the basis for development of propagating wave equations and permit estimation of the dissipation rate of kinetic energy. Dimensional analysis provides a methodological basis to derive Zakharov's equation (Zakharov, 1965) of spectrum evolution of LFP, which is in turn compared with empirical observations of spectrum evolution of LFP as a function of rats' running velocity (Sheremet et al., 2016). These results will be synthesized into a neural network model based on the Galves-Löcherbach model (Galves et al., 2013) for the CA3 region of the hippocampus with results compared to the neocortex.

Disclosures: Y. Qin: None. **A. Sheremet:** None. **A.P. Maurer:** None.

Poster

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Support: NIA R01 AG049722

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McKnight Brain Research Foundation

McKnight Brain Institute Postdoctoral Fellowship

University of Florida Research SEED Opportunity Fund

Title: Role of CA3 and dentate gyrus in the discrimination of perceptually similar objects depends on novelty of stimuli

Authors: *S. A. JOHNSON, S. M. TURNER, K. E. FERTAL, L. A. SANTACROCE, J. L. BIZON, A. P. MAURER, S. N. BURKE
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Abstract: Memory requires that similar episodes with overlapping features be represented distinctly. Notably, many symptoms of age-related memory loss appear to derive from the decreased ability to distinguish between similar events. In human neuroimaging experiments, discrimination of similar objects has been linked to activity in CA3 and dentate gyrus (CA3/DG; Doxey and Kirwan 2015, Yassa and Stark 2011), and discrimination impairments in the elderly correlate with altered CA3/DG activity (Yassa et al. 2011). Yet, work in animal models points to a critical role of the perirhinal cortex in distinguishing between similar visual stimuli (Bussey et al. 2005), and the requirement of CA3/DG in these tasks remains unexplored. We therefore asked whether neural activity in CA3/DG is required for accurate discrimination of a known target from lure objects. Adult male F344 x Brown Norway hybrid rats were shaped and trained to identify a target object (S+) in a forced-choice discrimination task, then surgically implanted with bilateral guide cannulae targeting dorsal CA3/DG. Rats were next tested on a target-lure LEGO object discrimination task in which feature overlap of a well-learned target object (S+) to lures (S-) was systematically varied (Johnson et al. 2017). The effect of reversibly inactivating CA3/DG on target-lure discrimination was first assessed within subjects in randomized blocks. Infusion of the $GABA_A$ agonist muscimol initially impaired discrimination of the target from distinct and similar lures (drug: $P<0.004$). On subsequent test blocks, however, performance improved across all overlap conditions irrespective of CA3/DG inactivation (drug: $P=0.37$). To clarify these results, a second experiment examined whether prior experience with stimuli influenced the effect of CA3/DG inactivation on object discrimination performance. Rats that received vehicle control infusions in a first test block, followed by muscimol, did not show discrimination impairments for target-lure pairs of any similarity (drug: $P=0.15$, similarity x drug: $P=0.42$). In contrast, rats that received muscimol infusions in the first test block were impaired across all target-lure pairs (drug: $P<0.0001$). Sustained efficacy of muscimol in silencing neural activity after repeated infusions was verified behaviorally and by absence of *Arc* mRNA in CA3/DG. Our results suggest neural activity in CA3/DG is most critical to complex stimulus discrimination when stimuli are novel. This is consistent with recent data suggesting dysfunction of the medial temporal lobe-hippocampal circuit, rather than hippocampus alone, contributes to age-related deficits in object discrimination.

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Poster

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Title: Beyond orienting: A role for mouse superior colliculus in memory-guided directional licking

Authors: *C. A. DUAN, S. K. FRUEKILDE, Y. PAN, T. ZHOU, N. XU
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Abstract: Survival in a dynamic environment requires animals to form and maintain decisions based on sensory evidence that may not be present at the time of decision execution. The ability to bridge past events with future motor actions has been studied using memory-guided perceptual decision tasks. Two regions that seem to be critical for these memory-guided tasks are the secondary motor cortex (M2) and the midbrain superior colliculus (SC). In monkeys and rats, M2 and SC are traditionally linked to planning saccades or orienting responses. Recent work in head-fixed mice have started to use directional licking as the choice effector in memory-guided tasks, and show that the anterior lateral motor (ALM) cortex in mouse M2 is important for planning licking responses. However, whether the mouse SC also participates in planning directional licking, as part of the distributed cortico-collicular circuit engaged by oculomotor and orientation systems, remains unknown. Understanding the neural control of directional licking is important because using this choice effector allows powerful experimental techniques that require both head-restraint and a mouse animal model.
To test cortico-collicular contributions to memory-guided licking, we developed a delayed auditory discrimination paradigm where head-fixed mice need to discriminate and categorize different rates of auditory clicks; form and maintain a motor plan during a delay period; and eventually respond by licking one of the two lick ports after a “Go” signal. Psychometric performance of well-trained mice was used to quantify the sensitivity and bias of their perceptual decisions. We then optogenetically inactivated SC or ALM neural activity during the sensory, delay, or choice period of the behavior in a within-subject design. Unilateral inactivation of SC or ALM activity resulted in a contralateral impairment and an ipsilateral bias in subsequent choices, especially after memory-period inactivation. A generalized linear mixed model was

used to compare the effect of inactivations in different brain regions, during different behavioral epochs, and between different trial types.
Having established the SC and ALM as foundational for memory-guided licking, we can now tackle circuit mechanisms underlying cortico-collicular interaction during motor planning. We will selectively silence ALM projections to SC or SC projections back to ALM via thalamus using chemogenetic synaptic silencing. These experiments will provide key insights to whether the information from SC back to cortex performs similarly important function as top-down cortical modulation.

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Poster

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Support: NIH Grant 1K99MH111926-01

Title: Economic choices reveal risk aversion and probability distortion in rats

Authors: *C. M. CONSTANTINOPLE[1], C. D. BRODY[2]
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Abstract: Humans evaluate economic options based on their utility, or the subjective satisfaction those options will provide (Von Neumann & Morgenstern, 1944). Additionally, humans exhibit probability distortion: we tend to overestimate the probability of unlikely events and underestimate the probability of likely events (Kahneman & Tversky, Econometrica, 1979; Stauffer et al., J Neuroscience, 2015). Utility and probability distortion account for many aspects of human choice behavior, but their neural basis is not understood. We have developed a high-throughput behavioral training approach for studying economic decision-making in rats, which reveals the utility and probability weighting functions of individual rats. Rats are presented with light flashes from the left and right side; these flashes convey the probability of receiving water reward at each port. Simultaneously presented auditory click rates convey the volume of water reward baited at each port. Rats thus make a choice between explicitly cued probabilistic gambles. Using a range of both reward probabilities and volumes allows evaluating utility and probability weighting functions. High-throughput training has yielded tens of thousands of choices per rat in 16 well-trained rats so far, enabling exploration of several parameters and conditions per animal. Subjects consistently maximize rewards and exhibit risk attitudes similar

to humans and monkeys. They also exhibit probability distortion, overweighting low probabilities. We present pharmacological and optogenetic inactivations and electrophysiology recordings from orbitofrontal, parietal, and frontal cortices (FOF). These experiments represent, to our knowledge, the first time that utility and probability distortion have been evaluated in rodents, enabling use of powerful tools to manipulate and monitor neural circuits underlying these phenomena.

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Poster

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Support: Howard Hughes Medical Institute

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Title: Rats can optimally accumulate and discount evidence for decision-making in a dynamic environment

Authors: *A. PIET, A. EL HADY, C. D. BRODY
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Abstract: How are choices made within constantly-changing noisy environments? The gradual accumulation of noisy evidence is considered to be a fundamental component of decision making. Previous work has characterized the evidence accumulation process in an environment with static statistics, finding that rats and humans can accumulate evidence with a memory time constant longer than the trial duration (Brunton, *Science*, 2013). However, complex decisions involve environments with statistics that change over time. In a changing environment, the optimal evidence accumulation strategy involves the additional task of discounting old evidence that may no longer inform the current state of the world (Glaze, *eLife*, 2015). We trained rats on an auditory decision-making task in a changing environment, to assess if and how rats can accumulate and discount evidence. Using high-throughput behavioral training and quantitative modeling, we find that rats can optimally discount evidence in a dynamic environment. The optimal timescale for evidence discounting is a function of the environmental variability, and the signal to noise ratio (SNR) of the noisy evidence. The SNR depends both on the noisy stimulus, and the subject's sensory noise. When accounting for sensory noise, the rats accumulate and discount evidence on the optimal timescale. Additionally, we demonstrate that individual rats rapidly adjust their discounting timescales in response to changes in the environmental

variability. Finally, we are now recording cortical spikes trains to analyze how dynamic integration variables are encoded within the brain.

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Poster

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Topic: H.01. Animal Cognition and Behavior

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Title: Dorsal hippocampal responses to gradual accumulation of evidence

Authors: *J. T. BOYD-MEREDITH[1], A. EL HADY[1], D. W. TANK[2], C. D. BRODY[3]
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Abstract: During spatial navigation, neurons in dorsal hippocampus of rodents have spatial firing fields that tile the environment, leading to the hypothesis that they represent a spatial map. Here, we use a non-spatial accumulation of evidence task in rats to query whether dorsal hippocampal neurons might represent a map of an abstract cognitive variable, namely, the gradually accumulating evidence. In a recent study, rats were trained to use a joystick to control the frequency of a sound stimulus, adjusting it toward a rewarded goal frequency [1]. Hippocampal cells had firing fields representing particular sound frequencies, leading the authors to speculate that the hippocampus plays a role in parametrically representing arbitrary behavioral states along task-relevant dimensions, with place representations being a special case of these more general representations. We aim to probe whether the hippocampus could develop fields representing behavioral state even when that state cannot be readily inferred from the currently observable environment. For example, accumulator fields could develop when an animal is accumulating evidence in favor of a binary decision. To test this hypothesis, we modified an already well-characterized accumulation of evidence task in which rats are required to orient toward a reward port on the left or right side that was associated with more pulsatile auditory stimuli [2]. In this task, the current state of the accumulated evidence is not determined by the instantaneous stimulus, which can only take three values (left click, right click, no clicks), but is instead determined by the accumulated history of the stimulus within the current trial. In order to detect cells that develop accumulator fields, we performed tetrode recording from dorsal hippocampus in rats trained in a version of the task in which, on each trial, evidence is gradually presented over long sustained nose pokes up to 8 seconds in duration. We observe hippocampal neurons whose firing rates are variably modulated during each epoch of the task including trial

initiation, stimulus presentation, orienting, and the intertrial interval. We will investigate whether this spiking activity occurs in fields linked to the value of the accumulated evidence, which would extend the notion of the hippocampal map beyond representations of the environment toward representations of an abstract, inferred state space.
1. Aronov, D., *et al.*, *Nature.* 543, 719-722 (2017).
2. Brunton, B., *et al.*, *Science.* 340, 95-98 (2015).

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Poster

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Title: Widespread cortical involvement in virtual evidence-based navigation

Authors: *L. PINTO[1], S. KOAY[2], S. Y. THIBERGE[3], D. W. TANK[2,3], C. D. BRODY[4]
[1]Princeton Neurosci. Inst., [3]Bezos Ctr. for Neural Dynamics, [2]Princeton Univ., Princeton, NJ; [4]Princeton Neurosci. Inst. and Dept of Mol. Biol., HHMI / Princeton Univ., Princeton, NJ

Abstract: The gradual accumulation of noisy sensory evidence for perceptual decisions is a key cognitive phenomenon, but much remains unknown regarding which areas are involved in it and what cortical activity patterns underlie it. To tackle these questions, we implanted VGAT-ChR2-EYFP mice with headplates and cleared their skulls, allowing optical access to the entire dorsal surface of the cortex. We then used a blue laser coupled to a 2D scanning galvanometer system to comprehensively and systematically inactivate discrete cortical patches during performance of a virtual navigation-based visual accumulation task with pulsed stimuli. Head-fixed mice navigated a T-maze in a virtual reality system to retrieve water rewards from one of the two arms. While they ran up the central stem of the maze (cue region, 200 cm), salient visual stimuli (towers) appeared transiently on either side, following spatial Poisson processes of different rates. After a delay region without any stimuli (100 cm), the mice made a turn to indicate the side with the highest total number of towers. Psychometric and logistic regression analyses revealed that the mice were sensitive to the difference between right and left tower counts, and that they used multiple towers across the cue region to make a decision (Pinto et al., SFN 2016). Bilateral, whole-trial silencing of several visual, association and premotor cortical regions resulted in

significant decreases in performance, observed in ChR2+ mice but not in controls. Finer temporal inactivations, however, revealed differential contributions. Inactivating the retrosplenial cortex (RSC) during the first half of the cue period affected performance in a similar fashion to not presenting towers in that period, whereas inactivating the posterior parietal cortex in the same period had no effect. Inactivation of the anterolateral portion of the premotor cortex also resulted in behavioral deficits, albeit differently than RSC - it induced earlier turns, potentially indicating interruption of the decision process. Inactivation of any of these three regions during the delay period impaired performance. To better understand the nature of cortical contributions to our task, we are currently performing widefield Ca2+ imaging through the cleared skull of mice transgenically expressing GCaMP6f. Preliminary findings confirm widespread cortical involvement, but with different areas being preferentially active during different task epochs. Together, our results suggest that evidence accumulation and decision making recruit large regions of cortex, but that specific cortical areas contribute to distinct yet overlapping aspects of the computation.

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Poster

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Title: The influence of mediodorsal thalamus on the development of prefrontal neuronal responses in rats learning the DNMTP task

Authors: *M. J. FRANCOEUR[1], E. K. BRASLEY[2], C. L. HOLLER[2], E. K. WARREN[2], N. MONTERIO[2], L. M. CALDERAZZO[2], K. HOWARD[2], B. M. GIBSON[1], R. G. MAIR[1]
[1]Psychology, [2]Univ. of New Hampshire, Durham, NH

Abstract: Interactions between mediodorsal nucleus (MD) and prefrontal cortex (PFC) support flexible goal-directed behavior. Behavioral studies have shown that both MD and PFC lesions impair the ability to learn and perform decision-making tasks like delayed non-match to position (DNMTP). Questions remain about how MD affects cellular activity in PFC. Previously we have examined how unilateral pharmacologic inactivation of MD affects the activity of medial PFC neurons in rats performing the DNMTP task. We found that thalamic inactivation disrupts signal-to-noise properties and event-related frequency spectrograms while reducing high frequency activity of PFC neurons. To test the hypothesis that MD lesions disrupt the acquisition of

complex decision-making tasks we lesioned MD in one hemisphere before rats were exposed to DNMTP. The lesions did not interfere with the ability of rats to learn and perform the DNMTP task. Once rats reached criterion for learning DNMTP we compared PFC activity from the ipsilesion and contralesion hemispheres using bilateral recording arrays of driveable tetrodes. We analyzed local field potentials, event-related activity, and spatial coding properties of PFC neurons. Our results confirm the findings of our earlier inactivation studies, showing the important influence of MD on PFC activity. They support the hypothesis that MD is fundamentally important for the acquisition of neural responses in PFC that mediate successful performance in the DNMTP task.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: DC 04845

Title: Inactivation of primate dorsolateral prefrontal cortex during auditory and visual working memory

Authors: *S. SHAH[1], B. PLAKKE[1], T. LINCOLN[1], K. KEVELSON[1], J. BIGELOW[2], L. M. ROMANSKI[1]
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Abstract: The prefrontal cortex (PFC) is an essential node in the process of working memory, as has been extensively established through neurophysiology, neuropsychology and neuroimaging studies, in both humans and nonhuman primates. A large proportion of the studies that have investigated the neural mechanisms of working memory, especially in nonhuman primates, have utilized only visual stimuli as the memoranda to infer neural processes. However, the frontal lobes are also important for language and communication, and therefore should demonstrate involvement in auditory working memory. Furthermore, large lesions of the lateral prefrontal cortex have been previously shown to disrupt auditory discrimination. In some recent studies and theoretical models based on results from studies of visual working memory, it has been suggested that dorsolateral prefrontal cortex (DLPFC) may play a process-oriented role, irrespective of modality. Investigation of the prefrontal cortex in auditory working memory is

therefore important to establish a broader understanding of prefrontal working memory functions and whether they are “amodal” in nature. Previous studies in our laboratory have shown that neurons in the ventrolateral prefrontal cortex (VLPFC) are active during audiovisual working memory. In these studies, rhesus macaques were trained in a delayed response paradigm with naturalistic face-vocalization stimuli as the memoranda. Our studies have also shown that inactivation of VLPFC with reversible cortical cooling, decreased performance of auditory working memory but not visual working memory. VLPFC inactivation included areas 12/47, 45 and part of area 46 ventral. In the current study we asked if inactivation of DLPFC would show similar effects as our inactivation of VLPFC or if there would be impairments unrelated to stimulus modality. We, therefore, inactivated the DLPFC in nonhuman primates performing an auditory and a visual delayed response task. Assessment of performance on each task during DLPFC inactivation will determine whether DLPFC plays a general role in working memory or a modality-specific function. These experiments will help us understand the differential (or possibly overlapping) contributions of dorsal and ventral prefrontal cortex to working memory across different modalities.

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Spain MINECO BFU2009-09537

Title: Activity-based and synaptic-based memories in prefrontal cortex during spatial working memory

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Abstract: Persistent activity of prefrontal neurons is thought to maintain locations in memory during the delay interval of working memory tasks. The bump-attractor model offers an elegant explanation for physiology and behavioral precision in delayed response tasks via diffusing bumps (Wimmer et al. 2014). This model can also naturally explain serial biases in this task, whereby previous memoranda interfere attractively with newly stored locations (Papadimitriou et

al. 2015). However, serial biases are only consistent with bump-attractors if instead of being reset after the report of the remembered stimulus at the end of a trial, the circuit keeps old memory representations as activity bumps through the inter-trial interval (ITI), so they interfere in the upcoming trial (Papadimitriou et al 2016). To address the neural basis of this interference, we analyzed behavioral and prefrontal neural data from monkeys performing an oculomotor delayed response task (Constantinidis et al. 2001). Monkeys showed a bias towards previous reported locations, which was attractive for previous saccadic reports near the currently memorized location, and repulsive for more distant previous reports. This could be explained by interacting bump-attractors (Almeida et al. 2015). However, single neuron dynamics was not consistent with this hypothesis: neuronal firing rates ceased to represent the previous stimulus in the ITI. Interestingly, ~500 ms before cue presentation single-neuron activity reflected a re-emergent activity bump (Papadimitriou et al 2016): we found significant tuning to the previous cue and negative noise correlations between pairs of neurons when the previous cue engaged them at opposite flanks of the bump (Wimmer et al. 2014). Since the previous stimulus code was temporarily absent and later reemerged, this finding pointed to a second mechanism holding latent information possibly at the synaptic level (Mongillo et al. 2008). This idea was supported by stimulus-selective cross-correlation peaks of pairs of neurons with similar memory fields, which persisted through the ITI. Thus, in the ITI the prefrontal network is still imprinted with previous memories, via two distinct but interacting memory substrates, one based on persistent activity during the delay and one based on functional connectivity changes during the ITI. Including short-term plasticity in the bump-attractor computational model, we matched this physiology, explained previous behavioral findings and derived predictions that we validated in human behavioral experiments.

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Poster

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Title: Inactivation of the rat parietal cortex impairs performance of a visuospatial, but not olfactory, working memory task

Authors: *G. A. SCOTT, N. K. ZABDER, A. J. ROEBUCK, Q. GREBA, J. G. HOWLAND
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Abstract: Working memory (WM) is the ability to temporarily store information for use and manipulation. WM likely depends on higher cortical areas including fronto-parietal circuits involved in executive function and attention, a view supported by ample evidence from human and non-human primate studies. Additionally, previous work in rodents has demonstrated a critical role of the medial prefrontal cortex (mPFC) in the performance of two WM tasks: the odor span task (OST; an olfactory incremental delayed nonmatching-to-sample task) and the trial-unique delayed nonmatching-to-location task (TUNL; a touchscreen-based visuospatial WM and pattern separation task). However, relatively little research has been conducted in rodents to elucidate the role of the parietal cortex (PC) in WM. We performed two separate experiments assessing the effects of inactivating the PC with the gamma-aminobutyric acid (GABA) receptor agonists muscimol and baclofen (M/B) on performance of the OST and TUNL in rats. 1) Bilateral infusions of M/B into the PC (AP -3.8-4.0, ML 2.2 and 3.4, DV -1.6; n=8) did not reduce the mean number of odors rats could remember in the OST, indicating intact olfactory WM capacity. In contrast, M/B infusions into PC (n=10) impaired performance in a positive control task, spontaneous cross-modal object recognition. 2) We assessed the effects of M/B infusions into PC on performance in the TUNL task. Infusions of M/B into the PC (n=4) significantly increased the number of correction trials rats performed. Impaired accuracy (~25% reduction) was also noted specifically at medium distances between the sample and test stimuli, although this effect did not reach statistical significance. Interestingly, infusions of the N-methyl-D-aspartate (NMDA) receptor antagonist AP5 had no effect on TUNL performance in the same animals, indicating that performance of TUNL may not rely on NMDA receptor function in the PC. These results suggest that olfactory WM is independent of the PC in rats, but that visuospatial WM may be mediated by the PC in rats, as has been found in primates. Thus, the role of the PC in WM may be sensory modality-specific. The results are notable given that research in primates has consistently found a role of the PC in WM when visuospatial WM tasks are used. Work to increase the sample size in the TUNL experiment is ongoing.

Disclosures: **G.A. Scott:** None. **N.K. Zabder:** None. **A.J. Roebuck:** None. **Q. Greba:** None. **J.G. Howland:** None.

Poster

080. Working Memory: How Memory Works

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 080.21/PP23

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH093354

Title: The contribution of muscarinic M1 receptors to working memory related neuronal activity in dorsolateral prefrontal cortex

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Abstract: The prefrontal cortex (PFC) subserves our higher cognitive functions, generating the mental representations needed for working memory. Acetylcholine (ACh) plays an important role in the memory functions of the PFC, and can act at both nicotinic receptors and muscarinic receptors. Our previous study revealed that in primate dlPFC, nicotinic a7 receptors (a7R) are concentrated within the postsynaptic density (PSD) of NMDAR synapses on layer III dlPFC spines, and ACh stimulation of a7R is permissive for NMDAR actions and essential for dlPFC Delay cell firing. Muscarinic M1 receptors (M1Rs) are also found in the PSD of glutamate synapses in layer III of dlPFC, where they may depolarize the synaptic membrane by closing synaptic KCNQ channels ("M" channels). We tested this hypothesis in the current study, using iontophoresis coupled with single unit recordings from monkeys performing an oculomotor, spatial working memory task. We found that iontophoresis of an M1R antagonist, reduced, while agonists enhanced dlPFC Delay cell firing, and co-application of an M1R antagonist significantly reversed the enhancing effects of the M1 agonist. In addition, stimulating M1R prevented the detrimental effects of NMDAR blockade on delay-related firing. Similar to the effect of M1R activation, blockade of KCNQ channels with XE991 significantly enhanced delay-related firing of dlPFC Delay cells. These results indicate that M1R stimulation is necessary for NMDAR actions in dlPFC, encouraging the development of M1R agonists as treatment for patients with cognitive disorders.

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Poster

080. Working Memory: How Memory Works

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Title: Cognitive impairment: Evaluation of spatial working memory in the rat model for Neurocysticercosis

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Abstract: Neurocysticercosis (NCC) is a parasitic disease caused by the *Taenia solium* larval stage (cyst) when it infects the central nervous system. NCC is the leading cause of acquired epilepsy in endemic countries. The clinical manifestations of NCC are pleomorphic, where the seizures are the most common clinical manifestation; however, also observed are intracranial hypertension, or cognitive decline. Several reports have observed that patients with NCC suffering from cognitive deficit involving multiple memory deficits or dementias in some cases. The aim of this study was to standardize the animal model to evaluate the memory and learning using T-maze task in a novel animal to NCC using rats that was developed in our laboratory. The Holtzman rats between 12 to 15 days after birth were intracranial infected with activated *T. solium* oncospheres or saline solution for control group. Later, we use behavioral tasks to measure the spatial working memory at 3, 6, 9 and 12 months after infection. Then 12 months on infection and the last behavioral task to measure the spatial working memory, the rats were anaesthetized and perfused transcardially. The brains were included in paraffin, sectioned in coronal form and stained. The results indicate that the rat with NCC had spatial working memory deficits that are statically significant compare to control group ($p<0.02$), using T-Maze task. This difference was observed at different times after infection (3, 6, 9 and 12 months). Were found a strong correlation between number of cysts and memory deficit ($r = -0.6318$, $p<0.0001$). The localization of cyst in hippocampus in the brain is associated with the memory deficit in infected rats ($p<0.0001$). Histological examination showed a layer of collagen tissue, infiltrate cells, perivascular infiltrate and gliosis in the surrounding the cyst. This study confirms the relationship between NCC and impairment cognitive represented as memory deficit. On the other hand, the results show that we can use rat with NCC as animal model to evaluate memory and learning and the animal model will help to carry out future work to understand what factors are mediating this cognitive deficit. In the future we hope to look for new treatment schemes to avoid or decrease this cognitive deficit.

Disclosures: **L.E. Baquedano:** A. Employment/Salary (full or part-time):; UNIVERSIDAD PERUANA CAYETANO HEREDIA. **D. Carrion:** None. **R. Gilman:** None. **A. Delgado:** None. **E. Bernal:** None. **D.G. Dávila Villacorta:** None. **R.P. Carmen:** None. **C. Gavidia:** None. **L. Aguilar:** None. **M.R. Verastegui:** None.

Poster

080. Working Memory: How Memory Works

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Topic: H.01. Animal Cognition and Behavior

Support: NSF Grant IOS 1257679

NIDA Grant R15 DA035478

Title: Adolescent social defeat disrupts working memory in adulthood: Consequences of reduced prefrontal cortex dopamine

Authors: *M. A. WEBER, S. R. DAVIES, M. J. WATT
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Abstract: Teenage bullying victimization is associated with greater prevalence of adult psychiatric disorders characterized by impaired executive function, particularly in the domain of working memory. This suggests disrupted development of the prefrontal cortex (PFC) dopamine (DA) system, as working memory performance follows an inverted-U shaped function reliant on DA release and activation of DA D_1 receptors in the PFC, being impaired when DA is either too low or too high. Male rats exposed to social defeat in adolescence (model of teenage bullying) show deficits in working memory performance along with decreased medial PFC (mPFC) DA activity in adulthood. We hypothesize that the impairments in adult working memory result directly from mPFC DA hypofunction caused by the adolescent defeat experience. To test this, we determined the effect of brief restraint on subsequent working memory, as this manipulation is known to evoke acute DA release in the mPFC. Adolescent rats underwent daily social defeat from postnatal day (P)35-39, while age-matched controls were exposed to novel environments in the absence of social aggression. In early adulthood (P56+), working memory was assessed using a novel object recognition task, with half of the subjects experiencing restraint for 20 min immediately prior to behavioral testing. As expected, previously defeated non-restrained rats displayed impaired working memory compared to non-restrained controls. In line with previous research, working memory in controls was impaired by acute restraint stress. However, the working memory impairment seen in defeated rats was reversed by brief restraint, suggesting that this acute stressor sufficiently increased mPFC DA release to restore performance to control levels. This implies a direct relationship between cognitive deficits and the mPFC DA hypofunction induced by adolescent defeat. To confirm this, we will block mPFC DA D_1 receptors pharmacologically, which should prevent both the improvement in working memory caused by restraint in previously defeated rats and the restraint-induced working memory deficits in controls. We will also determine if glucocorticoid receptor (GR) expression is increased following adolescent defeat, as GR-facilitated mPFC DA release could explain why restraint can

improve working memory in defeated rats despite their inherent reduction in tonic mPFC DA activity. Together, these findings will provide mechanistic understanding of how adolescent stress exposure can have a negative impact on cognition in later life.

Disclosures: M.A. Weber: None. **S.R. Davies:** None. **M.J. Watt:** None.

Poster

080. Working Memory: How Memory Works

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The Ontario Mental Health Foundation

N.S.E.R.C.

Title: Intra-PFC infusion of cannabidiol induces impairments in cognitive flexibility measured in a set-shifting task through serotonergic 5-HT1a receptor transmission

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Abstract: The prefrontal cortex (PFC) regulates multiple psychological processes including anxiety, sociability, attention, flexibility and cognition. Considerable evidence underscore its critical role in the development of various types of psychiatric disorders like phobias, depression or schizophrenia. The development of schizophrenia-like symptoms has been linked to chronic cannabis use and studies have found that cannabinoids exposure in healthy volunteers may induce positive, negative and/or cognitive schizophrenia-like symptoms. The cannabis plant produces multiple phytochemicals with tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most abundant. While systemic THC induces psychotomimetic symptoms via altering perception and disrupting working memory, CBD is devoid of such actions and may counteract THC effects if co-applied. Clinical and pre-clinical evidence demonstrates that CBD possess potent anti-psychotic and anxiolytic properties, however, it is not known if the beneficial properties of CBD extend to the otherwise healthy brain state, or are limited to pathological neuropsychiatric states. Here we tested the acute effects of intra-PFC CBD on anxiety, sociability, flexibility and cognition using a battery of behavioral methods. We show that intra-PFC CBD infusion did not modulate anxiety levels in elevated plus maze, open field or light dark box tests. In addition, social motivation and social recognition memory were left intact with

CBD treatment. In contrast, intra-PFC CBD impaired flexibility of animals tested in operant chambers during the set shift procedure. CBD infused rats needed more trials to complete the task and showed increased perseverance, reflecting a lack of cognitive flexibility and prolonged use of previously learned, ineffective response strategy. Additionally, CBD interrupted perceptual processes and latent inhibition measured with simultaneous oddity discrimination task and expression of conditioned fear respectively. Interestingly, CBD applied one day before auditory fear conditioning decreased expression of fear during the memory recall phase, confirming previously described anxiolytic effects of CBD. Impairments induced by intra-PFC CBD were prevented by co-application of NAD, a 5-HT1a receptor antagonist, suggesting that CBD can affect local PFC circuitry through serotonergic transmission mechanisms. In conclusion, our data suggests that local actions of CBD in the otherwise healthy PFC, can induce deficits in cognitive flexibility, perception and attention, and that the therapeutic benefits of CBD on PFC-dependent cognitive tasks may be limited to exposure during pathology.

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Poster

081. Learning and Memory: Physiology

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01NS079774

Title: Nature of memory engrams: Conserved wiring and computational logic of cell assemblies

Authors: *G. FOX[1], K. XIE[1], J. LIU[1,2], J. Z. TSIEN[1,2]
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Abstract: There is considerable scientific interest in understanding how memory engrams are organized so that the brain can generate specific perceptions and memories. Here, we propose the *Theory of Connectivity* that yields the basic wiring and computational logic for organizing the microarchitecture of memory engrams that permits the emergence of knowledge and flexible behavior. This concept is based on what we term the power-of-two-based, specific-to-general permutation logic. We suggest that at the level of cell assemblies, the brain is made of functional connectivity motifs (FCMs), and each FCM is made of neural clique assemblies arranged from specific input-coding principal cell assemblies to sub-combinatorial and to general convergent input-coding cell assemblies. We propose that this wiring logic should be carried out in many brain regions regardless of anatomical variation, and should also hold true for different cognitive

computing. Here, we test these predictions by using *in vivo* recording techniques to evaluate functional connectivity patterns of cell assemblies while animals are subjected to fearful stimuli. We show that this power-of-two-based permutation logic is widely used in cortical and subcortical circuits and is conserved for processing emotional information. Interestingly, this specific-to-general permutation logic remained largely intact although NMDA receptors—the synaptic switch for learning and memory—were deleted throughout adulthood, suggesting that the logic is developmentally pre-configured. Additionally, independent random-connectivity model analysis strongly indicate that that the specific-to-general permutation logic was constructed via the nonrandom strategy that is independent of learning in adulthood. Thus, these observations provide strong evidence that memory engrams are indeed organized via power-of-two-based permutation logic at the level of cell assemblies.

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Poster

081. Learning and Memory: Physiology

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Title: MCH neurons impair memory during sleep

Authors: *S. IZAWA[1], R. INOUE[2], S. CHOWDHURY[3], Y. MUKAI[2], A. YAMANAKA[4]
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Abstract: Melanin-concentrating hormone-producing neurons (MCH neurons) project widely throughout the brain from the lateral hypothalamic area. Although MCH neurons were initially supposed to be a feeding regulator, recent several studies showed its role in the regulation of sleep/wakefulness. Activation of MCH neurons using optogenetics increased time in rapid eye

movement (REM) sleep and these neurons are active during REM sleep were reported. However, its physiological role has not been fully understood so far. Here we examined possible involvement of MCH neurons in memory formation since MCH neurons densely innervate the hippocampus and septum where are known to be involved in memory. We used MCH neurons-ablated mice (Tsunematsu et al., J Neurosci 2014), and these mice were subjected to three different *behavioral tests related to recognition, spatial* learning and fear *memory, that is* novel object recognition test, Morris water maze and contextual fear memory test, respectively. MCH neurons-ablated mice showed significant improvement of memory in all three memory tests compare with control mice. To reveal whether the activation of MCH neurons during sleep affected memory, sleep was deprived during retention time. Sleep deprivation did not improved memory suggested that activation of MCH neurons during sleep was affected memory. To confirm this hypothesis, MCH neurons were activated using pharmacogenetics or optogenetics. Activation of MCH neurons during sleep significantly impaired memory formation. To reveal mechanism of memory impairment, slice patch clamp recording from MCH-channelrhodopsin2 (ChR2) mice was performed. Pyramidal neurons in the hippocampus were patch clamped and ChR2-expressing MCH neuron's nerve terminals were activated by blue light illumination. Activation of MCH nerve terminals hyperpolarized and decreased firing frequency of pyramidal neurons. Taken together, here we found that hypothalamic MCH neurons negatively regulates memory during sleep by inhibiting activity of hippocampal pyramidal neurons. This circuit could be a functional adaptation that effectively saves memory resources by inhibiting memories that are not important for survival.

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Poster

081. Learning and Memory: Physiology

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Topic: H.01. Animal Cognition and Behavior

Title: K_{ATP} gain-of-function mutations alter hippocampal neuronal excitability and severely impair spatial learning and memory in a mouse model of human DEND

Authors: *S. V. YAHIL[1], A. BENZ[2], H. CONWAY[3], J. GUNN[2], D. F. WOZNIAK[2], S. J. MENNERICK[4], M. S. REMEDI[3]
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Abstract: ATP-sensitive potassium (K_{ATP}) channels couple glucose metabolism to membrane excitability in neurons and insulin-secreting pancreatic β-cells. Gain-of-function (GOF)

mutations in the pore-forming Kir6.2 subunit of K_{ATP} have been identified as the leading cause of human neonatal diabetes, including a novel syndrome known as Developmental delay, Epilepsy, and Neonatal Diabetes (DEND). DEND associates with a host of neurological symptoms, including developmental motor delays, epileptic phenotypes, and mild to severe learning disabilities. Motor symptoms in DEND have previously been associated with K_{ATP} dysfunction in mouse cerebellar Purkinje neurons, suggesting a neuronal origin for the neurological disturbances, yet the etiology of learning and memory deficits remains elusive. Here we present behavioral and electrophysiological results from a novel mouse model of DEND. We have previously generated a Cre-inducible Kir6.2$^{[K185Q,\Delta N30]}$ (GOF) transgenic mouse. This mouse was crossed with a Syn-Cre line to express Kir6.2$^{[K185Q,\Delta N30]}$ under the synapsin promoter, thus targeting K_{ATP}-GOF mutations to neurons (Syn-K_{ATP}-GOF). Strikingly, Syn-K_{ATP}-GOF transgenic mice reiterated most of the neurological features of human DEND, exhibiting hyperactivity, sensorimotor deficits (balance/coordination), and profoundly impaired spatial learning in place and probe trials in the Morris Water Maze. To explore possible cellular mechanisms underlying the learning/memory deficits in Syn-K_{ATP}-GOF mice, hippocampal neurons were isolated and cultured for electrophysiological experiments. Whole-cell patch-clamp electrophysiology in dissociated Syn-K_{ATP}-GOF hippocampal cultures demonstrated changes in action potential frequency in response to rising current injections, suggesting disturbances in membrane excitability arising from K_{ATP} channel activity. Together, these provide a potential substrate for cognitive features of DEND.

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Poster

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Program#/Poster#: 081.04/QQ1

Topic: H.01. Animal Cognition and Behavior

Title: Physical properties of dietary lipids in early life contribute to growth rate and neurodevelopment in individually and socially housed mice

Authors: L. SCHIPPER[1,2], S. VAN HEIJNINGEN[2], E. M. VAN DER BEEK[1,3], *L. M. BROERSEN[1], G. VAN DIJK[2]
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Abstract: Breastfeeding is regarded as the gold standard to provide optimal nutrition supporting infant growth and neurodevelopment. The duration of breastfeeding as well as the specific dietary lipid quality of Human Milk (HM) may contribute to this effect. Indeed, the lipid

composition in Infant Milk Formula (IMF) has been designed to closely match that of HM. Here, we studied in mice whether another aspect of lipid quality in milk, i.e. the physical properties of lipid globules, may also contribute to the quality of growth and neurodevelopment.
We developed a concept IMF containing large lipid droplets coated by Milk Fat Globule Membrane derived phospholipids, resembling the physical properties and composition of HM lipids more closely without changing lipid content (e.g. omega 3/6 or saturated fat contribution). Male C57Bl/6j mice were provided with semi synthetic rodent diet containing either the Concept (CON) or Control lipid composition (CTR) from postnatal day (P)16 until P43. At P43, half of the mice were sacrificed, the remaining mice were switched to standard rodent diet (AIN-93-M) until dissection (P126). Mice were kept either individual (IND) or social (SOC, n=2 siblings per cage) from weaning onwards and body weight gain was closely monitored. During adolescence and adulthood the mice were subjected to a test battery targeting various behaviors and cognitive functions including novel object recognition, elevated plus maze and social interaction tests. After dissection, femur length and plasma corticosterone and (metabolic) hormones were determined.
While IND housing resulted in several behavioral and developmental changes compared to SOC housing, the CON diet improved adolescent growth and bone development and reduced adolescent anxiety and increased adult social interest compared to CTR irrespective of housing type. In addition, CON diet improved cognitive function in adulthood.
In conclusion, dietary exposure in early life to a diet containing a lipid structure that mimicks the structural aspects of HM lipid globules (increased lipid droplet size as well as PL coating) improved juvenile growth, bone length and neuro- development with some effects sustained into adulthood, regardless of the housing situation. These data suggest that these structural aspects of dietary lipids in the early diet are a relevant target to improve growth and neurocognitive development in infants.

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Poster

081. Learning and Memory: Physiology

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Program#/Poster#: 081.05/QQ2

Topic: H.01. Animal Cognition and Behavior

Support: NIA Grant R15AG052935

Title: Differential effects of continuous versus intermittent exercise on memory in C57BL/6J mice

Authors: *M. E. GIEDRAITIS, M. N. COX, O. V. POTTER, C. D. JOHNSON, M. G. CONNOLLY, S. R. BRUCE, R. A. KOHMAN
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Abstract: Voluntary exercise is known to enhance cognitive function and promote physiological changes in the hippocampus, but little is known about the effects of different schedules of exercise on hippocampus-dependent memory. In rodent models, animals are typically given continuous (i.e., daily) running wheel access for an extended period. Conversely, humans generally exercise on an intermittent, or every other day, schedule. The ideal duration and frequency of exercise for an experimental model comparable to humans is unclear. The present study directly compared the effects of continuous and intermittent exercise on memory in a fear-conditioning task in female C57BL/6J mice. Animals in the exercise and control groups were housed with or without a running wheel for 2 hours a day for 28 days continuously (C), 28 days intermittently (IS), or 56 days intermittently (IL). The inclusion of the IL group allows for evaluation of whether the schedule or total number of exercise days mediates the cognitive enhancing effects of exercise. Following exercise or control housing, memory will be evaluated in a contextual- and auditory-fear conditioning task by assessing freezing to the training context and auditory cue. While data collection are still in progress, it is expected that variations in the schedule and amount of physical activity will have differing effects on exercise-induced enhancements in memory.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NSC101-2320-B-182-040-MY3; CMRPD170423

Title: Negative regulation of dopamine D_3 receptor on hyperdopaminergia-mediated cognitive deficit

Authors: *P.-K. CHANG[1], H.-Y. LI[2], J.-C. CHEN[1]
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Abstract: Patients afflicted with bipolar disorder demonstrate significant impairment in episodic memory throughout their acute depressive and manic episodes. Over-activation of brain

dopamine (DA) system has been thought to underlie the pathophysiology of such episodic memory deficits. Thus, mice with reduced DA transporter (DAT) expression, DAT knockdown (KD) mice, displaying hyperdopaminergic phenotypes, were used to model this brain pathology in the current study. We found that DAT KD mice indeed exhibited impaired novel object recognition (NOR) memory as compared with the wildtype (WT) mice. Moreover, the impairment could be prevented by single FAUC365, a DA D_3 receptor (D_3R) selective antagonist, administration prior to the object learning. Using D3R knockout (KO)/DAT KD mice, we found that mice with these double mutants displayed comparable performance in NOR as the WT mice, suggesting that the devastating effects of DAT KD on mice' NOR performance can be prevented by deleting the D_3R. Furthermore, one GBR12909, a DAT blocker, injection was found to impair the NOR performance in the WT mice, but not in the D_3R KO mice. Finally, impaired NOR performance in GBR12909-treated WT mice was prevented by a pretreatment with FAUC365. These findings, taken together, prompt us to conclude that low-functioning DAT-induced over-activation of brain DA system may be involved in episodic memory impairment. Importantly, we for the first time show that D_3R seems to be necessary to mediate the low-functioning DAT-induced episodic memory impairment.

Disclosures: P. Chang: None. **H. Li:** None. **J. Chen:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

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JSPS Postdoctoral Fellowships for Research Abroad

Title: Neuronal activity in monkey prefrontal and posterior parietal cortex during foraging for object targets

Authors: *M. KADOHISA[1,2], K. WATANABE[1,3], M. KUSUNOKI[1,2], M. J. BUCKLEY[1], J. DUNCAN[2,1]
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Abstract: The prefrontal cortex (PFC) and posterior parietal cortex (PPC) which are reciprocally connected have been reported to show similar neuronal activity patterns while monkeys perform a memory-guided task. To address roles of the PFC and PPC during search for multiple

concurrent targets, monkeys were trained with object foraging tasks in which animals explored a choice array searching for targets in the first cycle (acquisition phase), and then exploited this knowledge in subsequent cycles (memory phase). The number of targets was one or two and foraging trials were repeated until the animal had touched all the target objects, then a cycle of the trials ended. On each trial, the objects of the search display appeared in random locations, necessitating choice based only on object identity.
In the acquisition phase, the animals searched the choice array by trial-and-error. In the memory phase, the animals' performance improved over successive cycles. While animals performed the foraging task, we recorded single unit activities in the PFC and PPC. We found many neurons of both PFC and PPC showed selectivity for the location of target objects to be touched. In both regions, selectivity became salient around 200-400 ms from the onset of choice array display, suggesting a parallel process of target discovery in the two regions. There was little effect of the number of targets in working memory, and little evidence in either region of neuronal activity tightly linked to motor preparation. With two targets in working memory, the data suggested competition for selection: While the activity of neurons which prefer the location of the selected target was enhanced, the activity of neurons which prefer the location of the unselected target was suppressed. The results suggest the PFC and PPC act in harmony, with a similar time-course and similar modulation by task conditions, to discover and select a target object in a choice array.
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Poster

081. Learning and Memory: Physiology

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 081.08/QQ5

Topic: H.01. Animal Cognition and Behavior

Title: Milk composition regulated by L-amino acid oxidase enzyme affect infant's brain development and function

Authors: *K. USUDA[1], Y. SHIGENO[2], G. WATANABE[1], S. TOMONAGA[3], K. NAGAOKA[1]
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Abstract: A number of studies have suggested a positive relation between breastfeeding and cognitive development of infant. Many components of milk provide biological benefits beyond basic nutrition for brain development during early life and their cognitive function in adulthood. In this study, we focused on one of amino acid metabolic enzyme, L-amino acid oxidase (LAO). We found that LAO expresses in lactating mammary gland and controls amino acid balance of milk by converting particular L-amino acids, such as phenylalanine and methionine. In addition, we investigate the influence of milk LAO for brain development and cognitive function using LAO knockout (KO) mice.
Metabolome analysis by GC/MS identified several differences of amino acid and its metabolite levels in milk between wild type (WT) and LAO KO. For example, WT milk contained low amount of phenylalanine and methionine but these amino acids accumulated in LAO KO milk. In other hand, phenylpyruvic acid and phenylacetic acid were significantly lower by LAO KO, suggesting that LAO contributes to phenylalanine degradation in milk. Next, we conducted behavioral analysis using adult WT and LAO KO mice. Spatial memory function in Morris water maze was decreased by LAO KO. To define the importance of milk LAO in the brain function, we investigated effect of cross-fostering within 24 h on the behaviors. It should be noted that decreased spatial memory function of LAO KO mice was rescued by feeding WT milk. To understand molecular mechanism, we analyzed gene expression difference in hippocampus from lactating infants and adults feeding WT or LAO KO milk by PCR based array in neurotransmitter receptor. The rescue of spatial memory function in LAO KO mice feeding WT milk was accompanied by increased *metabotropic glutamate receptor 5 (Grm5)* mRNA expression in adult hippocampus. In addition, mRNA expression of *oxytocin receptor* decreased in hippocampus of infants by feeding LAO KO milk, although there was no difference in *Grm5* mRNA expression. mRNA expression for genes involved in synaptic development (*Bdnf, CaMK2*) tended to be lower in hippocampus of infants by feeding LAO KO milk.
In conclusion, we revealed first evidence that milk LAO may play an important role in hippocampal development and memory function of infant. From the results of metabolome analysis and behavior analysis, altered phenylalanine metabolite levels in milk might affect the brain development and function through changing gene expression, especially Grm5 in mice hippocampus.

Disclosures: K. Usuda: None. **Y. Shigeno:** None. **G. Watanabe:** None. **S. Tomonaga:** None. **K. Nagaoka:** None.

Poster

081. Learning and Memory: Physiology

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 081.09/QQ6

Topic: H.01. Animal Cognition and Behavior

Support: Natural Science Foundation China (81671071 and 81471123)

Title: Associative memory extinction is accompanied by decays of associative memory cells and their plasticity at motor cortex but not sensory cortex

Authors: *J. H. WANG
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Abstract: Associative memory is essential for the cognition, which is presumably based on associative memory cells and their plasticity. Mechanisms underlying associative memory extinction versus its maintenance are still unclear, which we examine in a mouse model of cross-modal associative learning. Paired whisker and olfaction stimulations lead to a full establishment of odorant-induced whisker motion in training day ten, which almost disappears if paired stimulations are not given in a week and recovers after paired stimulations for an additional day. In mice of showing associative memory, extinction and recovery, we have analyzed the dynamical changes of associative memory cells and their plasticity in the barrel and motor cortices. Compared to control mice, excitatory synaptic transmission and spiking ability are upregulated as well as inhibitory synaptic transmission is downregulated at training day ten in associative memory mice. Without paired training for a week, these plastic changes are persistent in the barrel cortex and decayed in the motor cortex. This neuronal plasticity recovers in the motor cortex if paired training is given for an additional day to provoke associative memory. Moreover, the extinction and recovery of this associative memory are featured by the decay and reactivity of associative memory cells in the motor cortex, while associative memory cells in the barrel cortex are primarily for memory formation. Therefore, persistent neuronal plasticity in the barrel cortex for cross-modal memory maintenance as well as the dynamical change of neuronal plasticity in the motor cortex for memory retrieval and extinction. In other words, the sensory cortices are essential for long-term memory while the behavior-related cortices with the inability of memory retrieval are correlated to memory extinction.

Disclosures: J.H. Wang: None.

Poster

081. Learning and Memory: Physiology

Location: Halls A-C

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Program#/Poster#: 081.10/QQ7

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant K99DA041493

NIH Grant DA036534

Title: Optogenetic inactivation reveals multiple distinct roles for BLA in regulating risky decision making

Authors: *C. A. ORSINI[1], C. M. HERNANDEZ, III[2], S. M. SINGHAL[3], K. B. KELLY[4], C. J. FRAZIER[5], J. L. BIZON[7], B. SETLOW[6]
[1]UNIVERSITY OF FLORIDA, Gainesville, FL; [2]Neurosci., [3]Dept. of Pharmacodynamics, Col. of Pharm., [4]Dept. of Pharmacodynamics, [5]Pharmacodynamics, [6]Dept. of Psychiatry, Univ. of Florida, Gainesville, FL; [7]Neurosci., Univ. of Florida McKnight Brain Inst., Gainesville, FL

Abstract: Several psychiatric disorders are characterized by elevated risk taking and maladaptive decision making; however, the neural basis of risky decision making remains poorly understood. We showed previously that the basolateral amygdala (BLA) mediates decision making involving risk of punishment. In a Risky Decision-making Task (RDT), in which rats make discrete trial choices between a small, "safe" reward and a large reward accompanied by varying probabilities of footshock punishment, permanent BLA lesions increase choice of the large, risky reward in well-trained rats (Orsini et al. 2015, *J Neurosci*). The current experiments used an optogenetic approach to further elucidate how the BLA is recruited at different stages of the decision process. Rats received intra-BLA infusions of an AAV vector encoding halorhodopsin, followed by implants of intra-BLA optic fibers. Rats were then trained in the RDT until they reached stable performance. Laser stimulation occurred during three different choice trial epochs: 1) deliberation (the time between trial initiation and reward choice) 2) reward outcome and 3) intertrial interval (ITI). For the reward outcome epoch, there were three different stimulation conditions: a) during delivery of the small safe reward; b) during delivery of the large reward without punishment; c) during delivery of the large reward with punishment. A within-subjects design was used such that each rat underwent each type of stimulation session in a counterbalanced fashion. During deliberation, BLA inhibition decreased choice of the large, risky reward. During reward outcome, there was no effect of BLA inhibition during delivery of either the small, safe reward or the large, unpunished reward; however, BLA inhibition during delivery of the large, punished reward increased choice of the large, risky reward. Finally, BLA inhibition during the ITI had no effect. These data indicate differential functions of BLA during risky decision making: BLA activity during deliberation is required to bias choices toward risky (but also more beneficial) rewards, whereas BLA activity during receipt of punished rewards is required for the punishment feedback to bias choice behavior toward safer options. Moreover, the fact that BLA inhibition during delivery of either the small, safe or large, unpunished reward had no effect on choice behavior indicates that this structure is not critical for reward magnitude discrimination. Future studies will determine whether these different BLA functions are due to recruitment of different BLA target structures during risky decision making.

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Poster

081. Learning and Memory: Physiology

Location: Halls A-C

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Program#/Poster#: 081.11/QQ8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA036534

Title: Regulation of risky decision making by gonadal hormones

Authors: *S. L. BLAES[1], C. A. ORSINI[3], J. L. BIZON[4], B. SETLOW[2]
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Abstract: Many psychiatric diseases characterized by altered risk taking are differentially represented in males and females. The factors that govern sex differences in risk taking, however, remain poorly understood. Using a task in which rats make discrete trial choices between a small, “safe” food reward and a large food reward accompanied by varying probabilities of footshock punishment, we recently showed that females display reduced preference for the large, risky reward (i.e., are more risk averse) compared to males. The experiments herein were designed to test the extent to which these sex differences in risky decision making are attributable to differences in gonadal hormones. Intact male and female Long-Evans rats were trained in the risky decision making task until reaching a stable baseline of performance. Subsequently, males underwent either sham or castration surgery, and females underwent either sham or ovariectomy (OVX) surgery, followed by re-testing in the risky decision making task. In male rats, neither castration alone nor acute administration of testosterone (0, 0.75, 2.25, 7.5 µg) affected choice behavior. In contrast, in female rats, OVX caused a significant increase in choice of the large, risky reward (increased risk taking). To begin to evaluate the contributions of estrogen to this OVX-induced shift in choice behavior, sham and OVX female rats received acute injections of estradiol (E) either 2 months (0.0, 0.3, 5.0 µg) or 3 weeks (0.0, 5.0, 10.0 µg) after surgery. Surprisingly, E had no effect on choice behavior in OVX females at either post-surgical time points, whereas E increased choice of the large risky reward in sham rats at the 2 month time point. These data show that testosterone is not essential for maintaining risk taking behavior in males, whereas ovarian hormones appear to be necessary for maintaining lower levels of risk taking behavior in females. In addition, acute supraphysiological levels of E can also increase risk taking, an effect that may depend on the presence of other ovarian hormones and/or a normal complement of E receptors. Current studies are investigating these questions via administration of more chronic E regimens.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

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Program#/Poster#: 082.01/QQ9

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant RO1 AG016322

NIH Grant K18 AG048706

Title: Altered synaptic localization of C terminal splice variants of GluN1 subunits of NMDA receptors in the hippocampus of old mice with impaired spatial memory

Authors: *K. R. MAGNUSSON, D. R. ZAMZOW, V. ELIAS, V. ACOSTA, E. ESCOBEDO
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Abstract: The N-methyl-D-aspartate receptor (NMDAR) is important for memory formation and is particularly vulnerable to the effects of aging. The GluN1 subunit of the NMDAR has 8 splice variants. There are two C-terminal splice cassettes, C1 and C2. When C2 is spliced out, there is a new terminal sequence, C2'. Age-related alterations of splice cassette expression in the frontal cortex are associated with spatial memory impairments. In this study we explored whether changes in C-terminal splice cassettes in the synaptic and extrasynaptic membranes of the hippocampus were related to age-related spatial memory declines. Two ages of mice, 3 and 24 months, were behaviorally tested in the Morris water maze. The old mice were divided into two categories (good and poor learners), based on reference memory performance of young in place trials (threshold = mean + 2SD). The hippocampus from each mouse was subjected to differential centrifugation, followed by solubilization in Triton X-100. Proteins from Triton insoluble membranes (synaptic membranes), Triton soluble membranes (extrasynaptic membranes), and intracellular membranes/cytosol were examined by Western blot. Although old mice designated as good learners performed worse than young, the old mice assessed as poor learners were significantly worse than both the young and good old learners in place learning. The old good learners showed impairments in reversal trials, suggesting that improved memory in older individuals came at a cost of reduced flexibility. The significant changes in the GluN1 splice cassettes were confined to the old poorer learners. The protein expression of the C2 cassette was significantly higher in the old poor performers than the old good learners in the synaptic membrane of the hippocampus, but was reduced from young levels in the extrasynaptic membrane. In contrast, the C2' cassette was more prevalent in the extrasynaptic membrane in the old poor performers than both young and old good learners. There were no significant effects of age/learning ability on the C1 cassette or GluN2B or GluN2A subunit expression patterns in the hippocampus. These results suggest that there are alterations in the trafficking of NMDA

receptors in a subset of old mice that show the most impairment in spatial memory. These changes could impact synapse stability and NMDA receptor potentiation.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R37AG036800

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Evelyn F. McKnight Brain Research Foundation

Title: Elevated systemic expression of interleukin-6 modulates resting state functional connectivity in hippocampal and cortical areas

Authors: *M. FEBO[1], L. M. COLON-PEREZ[1], J. D. BARTER[2], B. YEGULA[2], P. CHAKRABARTY[2], A. KUMAR[2], T. C. FOSTER[2]
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Abstract: Interleukin-6 (IL6) has been shown to directly regulate neuronal firing and hippocampal synaptic plasticity (D'Arcangelo et al., 2000; Sallmann et al., 2000; Tancredi et al., 2000; Jüttler et al., 2002; Gruol, 2015). Several of these studies suggest an inhibitory effect of IL6 on synaptic transmission. Thus, systemic inflammation, which leads to increased expression of this pro-inflammatory cytokine, can potentially dampen neuronal activity in the hippocampus, as well as its extended functional circuitry, and affect cognitive function. Using adenoviral vector (AAV)-mediated expression of IL6 in rats, we tested whether increased systemic, low-grade, but sustained expression of IL6 affects functional connectivity within hippocampal networks and between hippocampus and other downstream cortical brain regions involved in learning and memory. We hypothesized that IL6 would reduce intrinsic hippocampal functional connectivity, as well as its synchronous activity with prefrontal/temporal/parietal cortical regions. Adult male Fisher 344 brown Norway rats (375-400g) were injected intramuscularly with either AAV-IL6 or AAV-EGFP as a control condition (n=8/group). Animals were imaged at 8 and 16 weeks following injection to allow expression and to monitor progressive functional brain changes over the course of expression. Scanning was carried out on a 4.7 Tesla MRI in rats

under a combination of 0.02 mg/kg dexmedetomidine/0.5% isoflurane. We used the following parameters for functional imaging: 2-segment spin echo-EPI sequence with repetition time = 1sec, echo time = 50ms, field of view = 3.2cm^2, data matrix = 64 x 64. We analyzed functional connectivity between 75 regions of interest in the rat brain using a fully segmented and annotated atlas. Control rats showed robust intrinsic functional connectivity in the hippocampus and intriguingly showed activity that was anticorrelated with the visual cortex. IL6 caused a slight increase in this connectivity and suppressed the anticorrelated activity. Additional analysis indicated that hippocampal functional connectivity with the temporal cortex and visual cortex was reduced by IL6. Interestingly, the rostral retrosplenial cortex, which is part of the default mode network as measured in rats, showed a greater connectivity with the anterior cingulate. Consistent with previous studies demonstrating a modulatory role of IL6 on synaptic transmission, we find that it also affects network level functional interactions, as measured by functional MRI.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

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Program#/Poster#: 082.03/QQ11

Topic: H.01. Animal Cognition and Behavior

Support: R37AG036800

RO1AG052258

RO1AG049711

McKnight Brain Research Foundation

Title: Influence of systemic inflammation on the transcriptional profile in the hippocampus

Authors: ***J. D. BARTER**[1], A. RANI[3], A. KUMAR[2], T. C. FOSTER[4]
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Abstract: Chronic systemic inflammation increases with age and is associated with cognitive impairment. To examine the role of systemic inflammation on cognition and brain function, young (5-7 months; n = 22) and middle-age (14-16 months; n=22) Fischer 344 Brown Norway hybrid rats were behaviorally characterized using water maze. Animals were matched for

performance and assigned vehicle or lipopolysaccharide (LPS, 1 mg/kg, i.p.) treatment (once per week for 6 weeks) to mimic chronic systemic inflammation. Seventy-two hours following the seven treatment, animals were re-tested for spatial memory performance and animals were sacrificed forty-eight hours after the final treatment. Pro-inflammatory cytokines were analyzed in the blood plasma and hippocampus. In the plasma, Eotaxin, IL-1β, MCP-1, and IP-10 significantly increased across age groups with LPS treatment, and IL-1β and IL-6 negatively correlated with memory across all age groups. LPS treatment significantly impaired memory performance in young ($p = 0.005$) animals. Next generation RNA sequencing was performed to determine treatment effects on transcription for the CA1 and dentate gyrus (DG) regions of the hippocampus from young animals. Across both regions, LPS treatment increased expression of inflammatory gene, C3. Statistical filtering and functional annotation clustering (DAVID) within each region indicated that LPS treatment decreased expression of ribosomal subunits in region CA1 and increased expression of neuron projection genes, including C4a, Nlgn2, and Mtor. LPS treatment increased expression of mRNA processing genes in the DG. These results indicate that chronic systemic inflammation influences cognition and brain gene transcription. Currently, we are processing hippocampal tissue from middle-age animals for RNA sequencing in order to address how chronic inflammation interacts with aging.

Disclosures: **J.D. Barter:** None. **A. Rani:** None. **A. Kumar:** None. **T.C. Foster:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R37AG036800

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Eveyln F. McKnight Brain Research Foundation

Title: Peripheral inflammation induces age-dependent attentional impairments in rats

Authors: *B. YEGLA, S. EIKENBERRY, T. C. FOSTER
Evelyn F. and William L. McKnight Brain Inst., Gainesville, FL

Abstract: Aging is characterized by increased inflammation, which correlates with cognitive decline. Activation of the peripheral immune system via acute lipopolysaccharide (LPS) injection elicits deficits in learning, spatial memory, and cognitive flexibility, with middle aged

rats displaying enhanced impairment. Little is known of inflammation's impact on vigilance, and more so, if systemic inflammation, which more closely models conditions in aging, impairs attentional function. Thus, we examined the impact of chronic LPS injections in young and middle-aged rats on the 5-choice serial reaction time task (5-CSRTT), expecting attentional deficits to emerge with chronic LPS treatment and greater disruption in middle aged rats. Young (4mo old) and middle aged (12-14 mo old) Fischer-344 rats were food restricted and trained on the 5-CSRTT, which requires continuous monitoring for a light cue (duration: 10, 2.5, and 0.5s) occurring in one of five holes and nose poking the lit hole. Once rats reached criterion (>50% correct on each signal duration and <10% omissions for five consecutive days) they were injected weekly with LPS (1mg/kg, i.p.) and their attentional capacity was assessed as a weekly average (four weeks total). The impact of treatment and age on attentional capacity were analyzed specifically. Rats were perfused and the prefrontal cortex (PFC), which significantly contributes to attentional performance, was assessed for activated microglia (Iba-1) and astrocytes (GFAP). After the first LPS injection, rats exhibited an exaggerated sickness response, which was observable in higher omission rates during the first week (interaction: $F_{1.64, 29.49}$=17.46, p=0.00). Average correct responses did not significantly vary by age ($F_{1,18}$=3.45, p=0.08) or treatment ($F_{1,18}$=0.24, p=0.63); however, for the shortest signal duration, aged LPS-injected rats displayed greater attentional deficits during the first week (p=0.05). All LPS-injected rats exhibited longer correct ($F_{1,18}$=6.75, p=0.02) and incorrect response latencies ($F_{1,18}$=12.29, p=0.003), despite no change in food retrieval latency, suggestive of LPS-induced cognitive slowing. In addition to attentional deficits, smaller, activated microglia in the PFC were observed after chronic LPS treatment (p=0.05), though GFAP density was comparable. Thus, peripheral inflammation impaired cognitive processing regardless of age and independently of the chronicity of treatment. As predicted, middle aged rats displayed greater attentional deficits under challenging conditions, though it arose immediately after infection and resolved with continued inflammatory activation.

Disclosures: B. Yegla: None. **S. Eikenberry:** None. **T.C. Foster:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

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Topic: H.01. Animal Cognition and Behavior

Support: R37AG036800

RO1AG052258

RO1AG049711

McKnight Brain Research Foundation

Title: Patch-clamp study of the mechanism for NMDA receptor hypofunction in CA1 hippocampal pyramidal neurons during aging

Authors: *A. KUMAR[1], J. S. THINSCHMIDT[2], T. C. FOSTER[3]
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Abstract: The age-related decrease in long-term potentiation during aging results from a decrease in Ca^{2+} influx through synaptic N-methyl-D-aspartate (NMDA) receptors. Studies that examine protein expression have described a decrease in GluN2B expression during aging; however, it is unclear if differential expression underlies decreases in synaptic NMDA receptor responses. In contrast, electrophysiological studies have described NMDA receptor hypofunction during aging, due to an oxidized redox state of neurons. The current studies employed whole-cell patch-clamp recording to investigate NMDA receptor hypofunction and the influence of redox state on NMDA receptor currents recorded from CA1 hippocampal pyramidal neurons in aged animals. Acute hippocampal slices were prepared from young (4-6 mo) and aged (24-26 mo) male F344 rats. Whole-cell patch-clamp recordings were performed to record synaptic responses in CA1 pyramidal cells elicited by stimulation of stratum radiatum. NMDA-mediated evoked synaptic currents were isolated following bath application of picrotoxin (20 µM) and DNQX (30 µM), and the isolation of NMDA currents was confirmed by bath application of the NMDA receptor antagonist, AP-5 (100 µM). The current-voltage relationship and input/output curves for the isolated NMDA receptor current indicated a decrease in the peak NMDA receptor currents in CA1 cells obtained from aged animals. The GluN2A selective antagonist, NVP-AAM077 (0.4 µM) and GluN2B specific antagonist ifenprodil (5 µM) decreased the NMDA receptor response to a similar extent in young and aged animals suggesting that a shift in the ratio of GluN2 subunits does not occur during aging. Similarly, the reduced peak NMDA currents in aged animals were not associated with a change in the decay rate of the synaptic response. In contrast, bath application of the reducing agent, dithiothreitol (DTT, 0.5 mm) increased peak NMDA receptor currents in cells from aged animals and slowed the rate of decay of the response in cells from both aged and young animals. These results demonstrate that redox state contributes to age-associated NMDA receptor hypofunction.

Disclosures: A. Kumar: None. **J.S. Thinschmidt:** None. **T.C. Foster:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

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Program#/Poster#: 082.06/QQ14

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R56AG049870

Title: Bump attractor network model predicts that age-related physiological changes contribute to spatial working memory impairments in the rhesus monkey

Authors: *S. IBAÑEZ[1], J. I. LUEBKE[2], P. R. HOF[3], C. M. WEAVER[1]
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Abstract: *In vitro* studies have shown that layer 3 pyramidal neurons from the dorsolateral prefrontal cortex (dlPFC) of rhesus monkeys undergo several changes with aging. For example, the frequency of spontaneous excitatory postsynaptic currents (PSCs) is lower in aged monkeys, while the frequency of spontaneous inhibitory PSCs is higher. Action potential firing rates are also higher in neurons from aged versus young monkeys. While these dlPFC pyramidal neurons are necessary for spatial working memory, the ways in which these physiological changes might affect behavioral tasks are not understood fully. As persistent activity in the dlPFC during the delay period of a spatial working memory task is thought to encode information about the stimulus, the perturbations of normal firing properties in aging may underlie the observed cognitive deficits. To test this hypothesis, we used a bump attractor model that generates persistent activity tuned to a specific angular preference (the 'bump'), even in the absence of external input. The model comprises 512 excitatory and inhibitory neurons receiving local recurrent excitation and broader feedback inhibition, with each neuron's output determined by a phenomenological activation function (AF) that describes its firing rate response vs. input current function. To simulate the functional changes that occur in the aged rhesus brain, we altered the strength of excitatory and inhibitory connections and the slope of the AFs in the model, and examined how these changes affected the bump activity. Increasing the AF for excitatory neurons without adjusting synaptic weights generally caused a fast loss of the bump, as all neurons began to fire together. When increasing the AFs of the excitatory and the inhibitory neurons, the network activity disappeared immediately after the cue period. We can still find instances for which the bump remains for the whole delay period, by adjusting combinations of the synaptic weights. Across the parameter space of the bump attractor model, we found a single connected region in which the bump activity was maintained until the end of the simulated delay period. The size of this region shrank when we increased the excitatory AF, even if compensated by changing the inhibitory AF. These results suggest that the physiological changes observed *in vitro* in neurons of aged vs. young monkeys lead to a loss of robustness of network function, making it harder for aged monkeys to succeed in this oculomotor working memory task.

Disclosures: S. Ibañez: None. **J.I. Luebke:** None. **P.R. Hof:** None. **C.M. Weaver:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

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Topic: H.01. Animal Cognition and Behavior

Support: Canadian Institutes of Health Research MOP-137072

Title: Functional remodelling of hippocampal VIP disinhibitory circuits during aging

Authors: *R. FRANCAVILLA, L. TOPOLNIK
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Abstract: Cognitive decline and memory deficits are considered the hallmark of the aging brain with cortical neuronal circuits representing the main target in aging-associated deterioration. While GABAergic inhibitory and disinhibitory circuits are at the basis of cognitive processes, their roles in age-related cognitive decline remain largely unknown. In particular, imbalanced inhibition and local hyperactivity of pyramidal neurons have been reported in the aged hippocampus (Bakker et al., 2012; El-Hayek et al., 2013), but the role of the interneuron-selective (IS) vasoactive intestinal peptide (VIP)-expressing interneurons in these processes remains unstudied. Using a combination of morphological analysis, whole-cell patch-clamp recordings in acute hippocampal slices and behavioural screening in VIP-eGFP mice, we examined the properties of hippocampal CA1 calretinin/VIP-co-expressing type 3 IS (IS3) cells and the fluctuations in the inhibitory drive at their postsynaptic targets across the animal life span. Our data showed that while the number and morphological parameters (soma area, total dendritic length and surface area, number of branching points) of IS3 interneurons remained unchanged, the amplitude and the duration of the action potential generated in these cells were significantly increased in aged mice. The age-dependent modifications in active membrane properties of IS3 interneurons occurred in parallel with an increased inhibition in their postsynaptic targets, and correlated well with spatial memory deficits in the object-place memory task. Our data indicate that while IS3 interneurons survive and preserve their morphology in aged animals, their physiological properties undergo specific modifications, which lead to an increased inhibition of interneurons that receive IS3 input. Collectively, this study provides new evidence on the increased inhibition of GABAergic interneurons that could contribute to the pyramidal cells hyperactivity and associated memory impairment in the aged hippocampus.

Disclosures: R. Francavilla: None. **L. Topolnik:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.08/QQ16

Topic: H.01. Animal Cognition and Behavior

Title: The role of peroxiredoxin 6 in pathogenesis of Alzheimer's disease

Authors: *T. PAIROJANA[1], S. PHASUK[1,3], P. SURESH[1], P. SHARMA[1], S. P. HUANG[2], N. PAKAPROT[3], S. CHOMPOOPONG[4], I. Y. C. LIU[1]
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles. Oxidative stress caused by excessive ROS levels are believed to be the most important mechanism that induces neuronal damage in AD pathogenesis. Peroxiredoxin 6 (PRDX6), a dual enzyme with Glutathione Peroxidase (GPx) and Ca^{2+}-independent phospholipase A2 (iPLA2) activity is expressed in several brain areas including the hippocampus. Previous studies have shown that Prdx6-iPLA2 is an essential molecule to activate NOX2, an enzyme located at the cell membrane to generate ROS including in glial cells. Although it has been revealed that PRDX6 is also increased in human brain of AD patients, the regulation of PRDX6 expression in AD pathogenesis is still unclear. Activating transcription factor 3 (*Atf3*) is a stress responded gene which has shown to be rapidly induced under oxidative stress and related to AD pathogenesis. Using transcription factor binding prediction (Promo 2.0) tool, we found that *Prdx6* has an ATF3 binding site on its promotor region. Additionally, our 3xTg mice show memory deficit associated with the upregulation of *Atf3* and *Prdx6* mRNA level. Thus we hypothesized that the upregulation of *Prdx6* is regulated by ATF3 and this upregulation of PRDX6 accelerates the progression of AD pathology via the activation of NOX2. In this study, we aimed to investigate the molecular mechanisms of Prdx6-iPLA2 in pathogenesis of AD. To achieve this aim, the 3, 6, 9 and 12-months-old 3xTg-AD mice were used and different behavior tests such as tail-flick, open field test and trace fear conditioning were conducted. After behavioral trainings, all mice were sacrificed for immunohistochemistry, protein and RNA extraction from the hippocampus. Our preliminary results showed that 3xTg-AD mouse at the age of 3, 6, 9 and 12 months showed normal sensory function when compared with age-match control (p >0.05). Locomotor function in 3xTg 9 and 12 months was significantly lower than the age- match control (p < 0.05). Consistent with previous studies, we also witnessed fear memory impairment in 3xTg-AD mice at 6, 9 and 12 months with abnormal learning ability curve when compared with their control, also the cue fear memory in 3xtg 6 and 9 months showing significant decrease in freezing percentage when compared with control (p = 0.033 and p =0.021, respectively) . Moreover,

memory impairment in 3xTg-AD mice was accompanied by the upregulation of *Prdx6* and *Atf3* ($p < 0.05$). Further experiments are necessary to investigate molecular mechanisms underlying Prdx6-iPLA2 activity in pathogenesis of AD.

Disclosures: **T. Pairojana:** None. **S. Phasuk:** None. **P. Suresh:** None. **P. Sharma:** None. **S.P. Huang:** None. **N. Pakaprot:** None. **S. Chompoopong:** None. **I.Y.C. Liu:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.09/QQ17

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant # AG046580

Title: Impact of cognitive performance and normal aging on transcriptomic changes in the prefrontal cortex of rats

Authors: *M. R. DUGGAN[1], S. JOSHI[1], Y. TAN[2], M. SLIFKER[2], M. WIMMER[1], V. PARIKH[1]
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Abstract: Although cognitive changes occur as a normal process of aging, it is not well understood why some subjects show enhanced vulnerability, while others exhibit resilience to age-related cognitive decline. The concept of cognitive reserve has emerged explaining enhanced capacity for functional compensation due to increased levels of mental activity during life as the likely cause of such variation; individuals with higher reserve are considered to be less susceptible to cognitive decline. However, the genetic contribution to cognitive reserve remains unknown. Here we investigated how cognitive exposure impacts gene expression in the prefrontal cortex (PFC), a brain region known to regulate higher cognitive functions including the control of attention, in young and aged rats. Briefly, young (3 months) and aged (22 months) male Wistar rats were trained in an operant signal detection task that required subjects to distinguish between signal and non-signal events to attain a reward. After reaching criterion (≥70% correct responses), animals were tested in a behavioral session that consisted of the presentation of visual distractors to constrain demands on attention. Following this testing session, brain tissue was dissected to isolate medial PFC and transcriptomic analysis was conducted using next generation RNA sequencing. Another cohort of young and aged rats that were exposed to the operant chamber in a time frame consistent with their performing counterparts but never trained on the task served as non-performing controls. In general, age-related upregulation of genes that govern innate immunity, inflammatory responses, and

complement activation was observed. A total of 252 transcripts (FDR 10%) were differentially expressed in the PFC of performing versus non-performing rats. Enrichment analysis revealed significant downregulation of gene clusters related to lectin-mediated complement activation and cytokine signaling. Interestingly, an interaction of aging and cognitive performance exhibited an upregulation of genes linked to extracellular exosome pathway. Moreover, the expression of genes in this pathway predicted attentional capacity. Taken together, these findings indicate that engagement in cognitive activity may have the capacity to ameliorate age-related functional deficits, potentially by altering exosomal trafficking and intercellular communication. These changes presumably suppress the transcription of immune and inflammatory response genes thereby providing a reserve mechanism that act as a buffer to combat structural and functional decline in aging.

Disclosures: **M.R. Duggan:** None. **S. Joshi:** None. **Y. Tan:** None. **M. Slifker:** None. **M. Wimmer:** None. **V. Parikh:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Training Grant AG000096

NSF Grant IOS1150292

NSF Grant BCS1439267

Intramural Research Program of the National Institute on Aging

Title: Hippocampal neural mechanisms underlying age-associated impairments in the memory for sequences of events

Authors: *J. S. ASEM[1], M. F. ALDOGHMI[1], M. H. KASSIR[1], N. B. T. MIRZA[1], N. N. CHMIELEWSKI[1], G. A. ELIAS[1], C.-W. NG[1], J. M. LONG[2], P. R. RAPP[2], N. J. FORTIN[1]
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Abstract: Temporal organization is a defining feature of episodic memory, as the memory for individual events includes information about when they occurred. In particular, the ability to remember sequential relationships among events or stimuli is shared by a variety of species, including humans, nonhuman primates, and rodents. Our laboratory has developed and validated a nonspatial cross-species paradigm to investigate the neural basis of sequence memory in

humans and rats. Using this paradigm, in collaboration with a human neuroimaging laboratory, we previously demonstrated significant impairments in sequence memory performance in older adult humans. In particular, relative to young controls, older participants showed poorer overall performance as well as a specific pattern of impairments across probe types. Critically, providing a comparable behavioral characterization in older rats is important for investigating the neural mechanisms underlying this age-associated memory impairment as well as offering a platform for testing the effects of potential therapeutics. To test the hypothesis that a similar pattern of age-associated impairments is present in rats, we tested young and aged rats (pre-screened for spatial memory impairment in the Morris water maze) in our nonspatial (olfactory) sequence memory task. We observed similar results as previously reported in humans, such that aged subjects showed poorer overall performance, with a specific pattern of impairments across probe types, the severity of which was associated with their pre-screened spatial impairments. In order to probe the underlying neural mechanisms, ongoing efforts focus on recording local field potential (LFP) activity from multiple regions as the same subjects perform the task, to test the hypothesis that the observed age-related behavioral impairments are associated with a reduction in LFP synchrony among hippocampal, entorhinal, and prefrontal subregions.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.11/QQ19

Topic: H.01. Animal Cognition and Behavior

Support: Intramural Research Program of the National Institute on Aging

NIH Grant AG 10606

Title: Disrupted network functional connectivity in aged rhesus monkeys with cognitive impairment

Authors: S. L. ROSSI[1], A. BAKKER[2], J. E. YOUNG[1], C. HEROLD[1], H. GU[3], H. LU[3], Y. YANG[3], E. A. STEIN[3], *P. R. RAPP[1]
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Abstract: Changes in network functional connectivity are a prominent feature of many age-related neurodegenerative disorders, including Alzheimer's disease. However, defining the border between changes attributable to aging and disease processes has proved challenging based on human investigation. We previously demonstrated that aged rats with memory impairment display widely distributed changes in functional connectivity with the retrosplenial cortex relative to both young subjects and aged animals with intact memory. Here we extended that analysis to a nonhuman primate model. Young adult (n = 11, mean age = 12.6 years) and aged (n = 12, mean age = 25.4 years) rhesus monkeys were tested on a standardized neuropsychological test battery that revealed age-related deficits in spatiotemporal working and recognition memory. Monkeys were lightly anesthetized using a protocol previously shown to preserve resting state BOLD signal (low-level isoflurane and dexmedetomidine), and animals were imaged on a 3T Siemens Trio scanner. Following stabilization and acquisition of T1-weighted structural scans for localization, six whole brain resting state Echo Planar Imaging volumes were acquired (5 minutes each, steps = 200, tr = 1.7s) over a total of 30 minutes. Resting state scans were pre-processed using established pipelines and co-registered to the D99 macaque template using AFNI. Independent component analysis was performed using FSL. Seed based analyses were performed using a major hub of the default mode network and a region strongly implicated in cognitive aging: the posterior cingulate cortex (PCC) and dorsolateral prefrontal cortex (dlPFC). For both seeds, aged monkeys displayed a distributed pattern of increases in cortical functional connectivity, including temporal, insular, frontal, and anterior cingulate regions. These findings indicate that age-related alterations in cortical network functional connectivity extend to the nonhuman primate and may contribute to risk for the development of neurodegenerative disease.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.12/QQ20

Topic: H.01. Animal Cognition and Behavior

Support: BBS Research Enhancement

Clark Foundation

Title: Altered Arc and hippocalcin expression reflect activity-dependent and intrinsic excitability mechanisms in hippocampal-dependent spatial memory in an aging model

Authors: *R. M. WILHELM, L. T. THOMPSON
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Abstract: Learning and memory consolidation induce plasticity, increasing intrinsic excitability (reducing Ca2+-dependent afterhyperpolarizations [AHPs]) in CA1 pyramidal neurons. Neurons from senescent animals with impaired memory show enhanced long-duration slow AHPs (sAHPs). The ion channels mediating sAHPs are unknown, but the calcium binding protein hippocalcin has been shown to gate sAHPs in rodent CA1. Synaptic plasticity during memory consolidation also rapidly upregulates activity-dependent expression of Arc/Arg3.1 (activity-regulated cytoskeletal gene). Arc expression is correlated with enhanced intrinsic excitability (reduced AHPs) in rat CA1 neurons. The role of these plasticity mechanisms in impaired spatial memory in aging is investigated here.
A continuous spontaneous alternation task, scoring individual performance in a novel spatial environment, allowed assessment of both spatial memory and protein expression in dorsal CA1 or CA3 of young (4-5 mo), middle- (12-13 mo), and old-aged (24-25 mo) FBN hybrid rats. For 12 min, rats freely explored an unrewarded plus maze. Young rats systematically visited all arms of the maze, distributing exploratory behavior without repeatedly returning to recently visited arms. Each set of 5 consecutive arm entries were assessed for alternations (4 unique arm entries) and perseverations (more than 1 repeated arm entry), and divided by the number of possible alternations or perseverations to quantify spatial memory.
Perseverations increased with age, and heterogeneity in alternations significantly increased in middle- and old-aged cohorts. To analyze relations between protein expression and memory impairment, rats with alternation scores for the first 12 arm entries (i.e. controlling for locomotor differences) within 1 SD of young rat performance were defined as unimpaired; those with alternation scores $\geq$ 2 SD below young rats as impaired. In dorsal CA1, Arc protein expression was significantly reduced in middle- and old-aged cohorts, while hippocalcin expression was significantly enhanced. In control rats (no exploration), increased hippocalcin expression and decreased basal Arc expression was also seen with increasing age. In CA3, no age- or memory-related trend was observed for either hippocalcin or Arc expression.

Disclosures: R.M. Wilhelm: None. **L.T. Thompson:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NIH T32-AG049688

NIH AG010606

NIH AG016765

NIH AG006647

NIA Intramural Research Program

Title: The effects of aging on spine type and density on layer III pyramidal cells in area 7a of the intraparietal sulcus of behaviorally characterized primates

Authors: *S. E. MOTLEY[1,2,3,4], D. DUMITRIU[1,2,3], W. G. M. JANSSEN[1,2], P. R. RAPP[5], J. H. MORRISON[1,2,3,4,6]
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Abstract: Aging is associated with decreased working memory performance, and the integrity of this cognitive domain has been assessed using the delayed response (DR) task. Critically, this task has a delay period during which the presented stimulus is absent and the animal must retain task-relevant information in memory until the delay ends. The firing of a subset of pyramidal cells in area 46 of the prefrontal cortex (PFC), termed "delay cells" because of their firing during the delay period, has been shown to correlate with DR behavioral performance. It is proposed that this persistent firing maintains information across the delay, and disruption to delay cell firing impairs behavioral performance. Another correlate to DR performance is density of thin spines on layer III pyramidal cells in area 46. In aging, loss of thin spines correlates with decreased DR performance. It is proposed that thin spines in the PFC contribute to working memory because their instability would allow for rapid, experience-dependent remodeling of a circuit. Very little is known about age-related effects on working memory outside of the PFC. Area 7a of the intraparietal sulcus (IPS) projects to area 46 and, like area 46, has cells whose firing during the delay period correlates with DR performance. It is unknown if thin spines in area 7a are critical for DR behavioral performance, or if there are age-related changes to spines in this region. To better understand the role of the IPS in working memory and how age-related changes to this region affect behavioral performance, we have investigated differences in spine type and density in layer III pyramidal cells of area 7a in the IPS of young and aged, male and female, rhesus monkeys (Macaca mulatta) that were behaviorally characterized using the DR task. These data will be compared against our evolving model of a healthy synaptic profile to further define the effects of cognitive aging and the morphological changes across the brain that are associated with cognitive decline.

Disclosures: S.E. Motley: None. **D. Dumitriu:** None. **W.G.M. Janssen:** None. **P.R. Rapp:** None. **J.H. Morrison:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5F32AG046106-03

NIH Grant 5R01AG034446-07

Title: Activation of $G_{\alpha q}$ signaling prevents age-related cognitive decline

Authors: *R. AREY[1], G. STEIN[2], R. KALETSKY[1], C. T. MURPHY[3]
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Abstract: Over the past century, the increase in the population of elderly individuals has led to the emergence of age-related cognitive decline as a significant public health threat. It is therefore critical to not only develop therapies that prevent cognitive decline, but interventions that can improve memory performance in aged individuals whose cognitive function is already impaired. To study learning and memory, we developed positive olfactory association assays that pair a conditioned stimulus (CS) with an unconditioned stimulus (US) to measure short/intermediate-term (S/ITAM) and long-term (LTAM) associative memory in the nematode worm, *C. elegans*. Here we have identified a constitutively active mutant in the $G_{\alpha q}$ signaling pathway that forms a long-term (CREB-dependent) memory following S/ITAM training (1 CS-US pairing) in young adult animals, which usually requires 7 CS-US pairings. This is due to increased CREB transcriptional activity in the AIM interneuron pair, which we previously found to be the site of CREB activity during LTAM formation, resulting in mutants that are “primed” for memory consolidation. Surprisingly, altering $G_{\alpha q}$ signaling in a single chemosensory neuron is sufficient to cause a CREB-dependent memory extension following a single CS-US pairing, indicating a cell non-autonomous role for this pathway in enhancing memory circuit function. Activation of this pathway also appears to ameliorate age-related deficits in associative memory; animals with active $G_{\alpha q}$ signaling globally or in the AWC sensory neurons maintain their ability to remember following 1 CS-US pairing at an age when wild-type animals no longer exhibit LTAM following 7 CS-US pairings. Furthermore, temporally restricted activation of $G_{\alpha q}$ specifically in aged animals improves their memory performance, indicating that memory function can be rescued at an age where cognitive decline has already occurred. Maintenance of CREB activity in the AIM correlates with improved memory function in aged animals, which is in agreement with previous findings that CREB levels and activity are predictive of memory performance with age. These findings suggest that activation of $G_{\alpha q}$ in the AWC sensory neurons non-autonomously induces consolidation after a single CS-US pairing, bypassing the spaced training normally required for

LTAM formation, and enables the maintenance of cognitive function with age. Understanding the mechanisms by which $G_{\alpha q}$ signaling improves memory performance and increases CREB activity will enhance treatments to maintain and repair memory function lost with age-related cognitive decline and neurodegenerative disease.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

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NIH/NICHD R01HD083181

The Stedman West Foundation

Texas Children's Hospital

Title: Sustained ERK1/2 activation in oligodendrocytes of the developing CNS enhances hippocampal-mediated contextual fear memory in aged mice

Authors: *M. A. JEFFRIES[1,2], C. S. WARD[4], S. SORIANO[4], S. VEERARAGAVAN[4], A. J. LIANG[4], T. L. WOOD[5], S. L. FYFFE-MARICICH[3], R. C. SAMACO[4]
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Abstract: Cognitive decline during aging correlates with loss of integrative function within the brain. Importantly, connectivity and integration in the central nervous system (CNS) is dependent on the precise tuning of action potential propagation by insulating myelin sheaths. Pathological myelin structure, myelin degeneration, and decreased conduction velocity in the CNS have been observed in aged rodents and primates, and recent studies suggest a link between myelin abnormalities and conditions associated with neurodegeneration. While oligodendrocyte precursor cells (OPCs) in the CNS can generate new oligodendrocytes (OLs) throughout aging,

the resulting myelin sheaths are characteristically shorter and thinner than those produced by developmentally-generated oligodendrocytes. Here, we test the hypothesis that promoting increased myelin production by mature OLs during development leads to enhanced CNS function in aged mice.
Studies have shown that extracellular signal-regulated kinase (ERK1/2) signaling is a key regulator of myelination in the CNS. Specifically, sustained activation of ERK1/2 in mature OLs of the adult mouse CNS results in global hypermyelination, increased conduction velocity, and enhanced contextual fear memory at 4 months of age. We found that aged mice genetically induced to sustain ERK1/2 activation in OLs during the second postnatal week exhibited enhanced hippocampal-dependent contextual fear memory, yet displayed normal performance in behavioral evaluations for anxiety-like behavior, spontaneous exploratory activity, motor coordination and motor learning, sensorimotor gating, repetitive behavior, sociability, learned helplessness, and pain nociception.
Sustained ERK1/2 activation in OLs during development did not alter numbers of mature OLs, consistent with previous findings in adulthood. Interestingly, myelin thickness was similar to controls in developmentally induced mice at either 21 days post-injection of tamoxifen (dpi) or 2 months post-injection (mpi) in the corpus callosum. Current work is underway to examine whether enhanced hippocampal-dependent contextual fear memory in aged mice correlates with myelin thickness and/or ultrastructure changes in the hippocampus. Taken together, these results demonstrate that OL-specific ERK1/2 signaling selectively enhances hippocampal-dependent contextual fear memory while sparing multiple behavioral domains, suggesting that targeting ERK1/2 signaling in a cell-autonomous manner may potentially serve as an avenue for therapeutic intervention for cognitive decline.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.16/RR2

Topic: H.01. Animal Cognition and Behavior

Title: Physical exercise elicits hippocampal structural and functional changes in the aged murine brain

Authors: *X. ZHOU, D. G. BLACKMORE, P. F. BARTLETT
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Abstract: Objective: Physical exercise induces hippocampal volume and blood flow increase, leading to enhanced learning and memory in mice in early adulthood (Biedermann, et al. 2012;

Cahill, et al. 2015; Fuss, et al. 2014). However, whether exercise initiated in late adulthood, when the hippocampus tends to deteriorate, is able to improve the hippocampal status is unknown. The aim of this study is to determine whether physical exercise can robustly benefit the hippocampus in the very aged mouse brain both structurally and functionally.
Methods: We used a randomised controlled trial with sixteen 24-month-old female C57BL/6 mice, assigned to undergo either voluntary exercise on a running wheel or no exercise serving as a controls. In vivo T2-weghted imaging, diffusion tensor imaging and resting state functional imaging were performed using a 9.4T MRI scanner. Spatial learning was conducted using an active place avoidance paradigm.
Key findings: Following exercise, mice displayed significant changes in both structure and function in hippocampus when compared to controls. Physical exercise increased hippocampal volume by 2%, from 15.00 ± 0.071 mm^3 before exercise to 15.31 ± 0.075 mm^3 after exercise, effectively offsetting age-related volume loss. Physical exercise retains hippocampal microstructural integrity by a decreased mean diffusivity (MD) value in the hippocampus formation, changes consistent with increased cell density, suggesting that exercise protects against cellular death. Physical exercise strengthened hippocampal dynamics by increasing hippocampal BOLD signal functional connectivity, indicating that exercise strengthens communication within hippocampus. We also demonstrated that these detected changes positively correlated with cognitive performance.
Conclusion: These findings provide the first evidence that exercise is effective at changing both the structure and function of the hippocampus in late adulthood, which is accompanied by improved spatial learning ability. The understanding of exercise in this perspective will help fight against age-related hippocampal dysfunction.

Disclosures: X. Zhou: None. **D.G. Blackmore:** None. **P.F. Bartlett:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

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Program#/Poster#: 082.17/RR3

Topic: H.01. Animal Cognition and Behavior

Support: Research Program of the NIA AG10606

Title: GABAergic basal forebrain integrity is compromised in aged monkeys with cognitive impairment

Authors: *C. BANUELOS[1], K. H. SCHULZE[2], J. R. KITTLESON[3], J. M. LONG[4], E. J. PEREZ[2], S. FONG[5], M. T. ROBERTS[5], P. R. RAPP[6]
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Abstract: The search for strategies to promote optimally healthy cognitive aging has taken on increased urgency as people live longer. Basal forebrain projections to the cortex are anatomically positioned to influence a broad range of cognitive capacities including attention, executive function and memory. Although a long history of research on neurocognitive aging has focused on the role of the cholinergic basal forebrain system, intermingled GABAergic cells are numerically as prominent and well-positioned to regulate the activity of their cortical projection targets, including the hippocampus and prefrontal cortex. The effects of aging on the non-cholinergic basal forebrain in primates, however, are largely unknown. In this study, we conducted quantitative morphometric analyses in brains from young adult rhesus monkeys (n=8, mean=10.1 years), and aged animals (n=16, mean=32.1 years) that displayed significant impairment on standard tests that require the prefrontal cortex and hippocampus (i.e., delayed response and delayed nonmatching-to-sample; DNMS). Cholinergic (ChAT+) and GABAergic (GAD67+) neurons were visualized by immunocytochemistry in evenly spaced histological sections through the medial septal nucleus (MS), nucleus of the diagonal band (nDB), and the nucleus basalis of Meynert (nBM). Distinct GABAergic cell groups were co-extensive and partially intermingled among cholinergic neurons throughout the basal forebrain, spanning over 14 mm in the rostrocaudal axis, emerging in the MS and nDB and continuing through the caudal portion of the nDB. Whereas cholinergic neurons tended to be clustered, GABAergic neurons were more homogeneously distributed throughout the regions of interest. Morphometric quantification revealed a significant decrease in GAD67+ cell number in the basal forebrain of aged monkeys compared to young (p=.044). Parallel counts in adjacent sections demonstrated that ChAT+ cell number is preserved in the aged monkey basal forebrain. Additionally, GAD67+ neuron volume was increased selectively in aged monkeys that performed on par with young on the DNMS task, (p=.023). This effect may represent compensatory mechanisms resulting in preserved visual recognition memory at advanced age. These findings raise the possibility that GABAergic basal forebrain integrity represents a novel target for efforts to promote healthy trajectories of cognitive aging.

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Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.18/RR4

Topic: H.01. Animal Cognition and Behavior

Support: CAPES (Science Without Borders)

Title: Exercise has a persistent effect on learning and memory throughout the lifespan: The role of new neurons, inflammation and the cognitive reserve hypothesis

Authors: *B. C. MOTA, R. HENNESSY, Á. KELLY
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Abstract: Introduction: Age-related changes in brain plasticity and the effect of age on cognitive performance have been widely studied. It is known that age-related cognitive deficit in humans is influenced by early age experiences, and thus lifestyle factors and behaviours from early to middle age are likely to contribute to cognitive reserve in later life. In this context, studies have shown that regular physical exercise can stimulate brain plasticity and thus physical exercise at different stages of the lifespan may be a mechanism that protects against deleterious effects of ageing. **Aim:** To investigate the effects of exercise, initiated in youth until middle age, on learning and memory and plasticity in ageing. **Materials and Methods:** Young male mice (3 months) underwent treadmill running for a period of 8 months. At 11 months old, they ceased exercise and were housed in the absence of exercise until old age (21 months). Mice were tested every 2 months in the Novel Object Recognition (NOR) and Object Displacement (OD) tasks. Also, at 20 months old, they were assessed in the Morris Water Maze (MWM), tail suspension (TS) and the Elevated Plus Maze (EPM) tasks. Mice underwent Magnetic Resonance Imaging (MRI) and were euthanatized. Brain samples were stored for later analysis. **Results:** Behavioural analyses showed differences in the performance of both tasks (OD and NOR) between Exercise (EX) and Sedentary (SED) mice after 4, 6 and 8 months of exercise. Interestingly, even 9 months after exercise cessation, performance in the NOR, OD and MWM tasks was better in EX compared to SED mice. Also, EX mice showed decreased immobilization time in the TS task and less anxious behaviour in the EPM task. PCR analysis of hippocampal tissue revealed age-induced increases in IL-1B and TNF-a mRNA expression in SED mice that was prevented by exercise. Moreover, age-related increase in the mRNA expression of GFAP and Cd11b was observed in both groups, indicating that exercise prevented at least some of the inflammatory changes in the brain that are associated with ageing. Neurogenesis was assessed by immunohistochemistry and a significant difference was found in the number of positive BrdU cells and positive BrdU/NeuN cells in EX compared with SED group. **Conclusion:** Behavioural data suggest that 8 months of exercise enhances spatial and non-spatial memory and this enhancement can still be observed even 9 months after exercise cessation. PCR analyses suggest that exercise can modulate the inflammatory profile in the hippocampus of the aged mouse. Also, an increase in positive BrdU/NeuN cells indicates that exercise promotes newborn cell survival even 9 months after exercise cessation.

Disclosures: B.C. Mota: None. **R. Hennessy:** None. **Á. Kelly:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.19/RR5

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIA Grant AG009973

Phyllis F Albstein Fund for Research on Aging and Dementia

Title: Elevated inhibitory control is associated with intact cognition in aging across a hippocampal-cortical network

Authors: *A. BHAMMAR, R. P. HABERMAN, A. E. BRANCH, G. BLAIR, M. GALLAGHER
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Abstract: Excess neural activity in the hippocampus and interconnected cortical networks is associated with cognitive impairment and increased risk for Alzheimer's dementia in elderly individuals. The accumulation of amyloid-β (Aβ) containing plaques in prodromal Alzheimer's disease (AD) and a demonstrated association between Aβ and neural excitability in AD animal models suggest that altered production of Aβ may be associated with elevated neural excitability. The present study leverages a unique rodent model of neurocognitive aging in which neural excitability in aged subjects correlates tightly with increasing severity of cognitive impairment, independent of other pathological markers or neurodegeneration specifically associated with AD. We investigated whether increased expression of the precursor of Aβ (App) is associated with neural excitability in aged rats with memory impairment (aged impaired, AI) relative to both young adults (Y) and aged rats with memory performance on par with young (aged unimpaired, AU). We pharmacologically induced neural activity in cognitively characterized aged and Y rats and examined App and Gad1 expression, as measures of excitability and inhibition respectively, using quantitative in situ hybridization and semi-quantitative immunohistochemistry. We found significantly reduced App expression in AU rats relative to AI and Y in the CA3 subfield of the hippocampus and in the retrosplenial and parietal cortices, regions of a posterior cortical network functionally interconnected to the hippocampus. When assessed in conjunction with Gad1, we found the ratio of Gad1 to App mRNA, a measure of inhibitory/excitatory balance, was increased in AU rats relative to AI in all assessed regions. Of further interest in the context of preclinical and clinical research, AI rats treated with Levetiracetam, an antiepileptic with demonstrated ability to improve memory in aged impaired subjects, had an increased Gad1 to App ratio across the hippocampal/cortical network relative to untreated AI rats, mimicking the condition observed in aging with preserved memory function. While AU rats appear to naturally control excitability by upregulating Gad1 and downregulating App, this adaptation can be promoted in AI rats by

targeting over activity with Levetiracetam. A failure of inhibitory control in AI is evident not just in the hippocampus, but extends to cortical circuits interconnected with the hippocampus, where localization of overactivity coincides with sites of pronounced cortical amyloid deposition in early prodromal phases of AD.

Disclosures: A. Bhammar: None. **R.P. Haberman:** None. **A.E. Branch:** None. **G. Blair:** None. **M. Gallagher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AgeneBio, Inc.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.20/RR6

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIA Grant AG009973-22

Title: Enhanced inhibitory engagement with hippocampal activation by aged rats with preserved memory function

Authors: *R. P. HABERMAN[1], A. MONASTERIO[1], A. E. BRANCH[1], G. BLAIR[1], G. RAO[2], J. J. KNIERIM[2], M. GALLAGHER[1]
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Abstract: In a manner similar to elderly humans, aged outbred Long Evans rats exhibit individual differences in cognitive outcomes, including both intact and impaired memory function. Aged rats with preserved function (aged unimpaired, AU) perform on par with young adult (Y) rats on hippocampal-dependent memory tasks and are distinguished from old rats that perform worse than Y (aged impaired, AI). Because previous neurobiological studies have indicated that AU rats exhibit distinct gene expression profiles relative to both Y and AI rats in the hippocampus, the mechanisms underlying memory function in AU subjects may reflect an adaptive basis for resilience in neurocognitive aging. In response to a behavioral task previously used to engage hippocampal functions critical to memory formation, the present study examined gene markers for neural activation, synaptic plasticity and inhibitory control, processes that are compromised in aged individuals with impaired memory. Y and AU rats performed a cue mismatch task in which familiar cues were rearranged in a test session (change condition). Head scanning, a behavioral measure associated with information encoding of a subjects' environment, significantly increased in both Y and AU rats in response to the *change condition.* In contrast, AU and Y behavioral controls that experienced the same environment with cues retained in the familiar orientation (no change condition), did not show increased head scanning. Specific gene

induction was assessed by quantitative in situ hybridization in subfields of the hippocampal formation analyzed by comparing the *change* and *no change* conditions in the Y and AU groups. Zif268, a marker of neural activation, showed equivalently increased induction in the cue *change condition* in AU and Y groups relative to *no change* in all subfields (dentate gyrus-DG, CA1, CA3), supporting intact hippocampal activation in AU rats similar to Y. Based on previous gene array data, Nlgn1 and Camk2a were examined as learning-induced synaptic markers in the CA3 subregion and similarly exhibited increased induction in the *change condition* in both AU and Y rats. In contrast, Gad1, a marker for inhibitory control, was a distinctive signature in the *change condition* with a significant increase only in AU rats in both the DG and CA3 regions of the hippocampal formation. This finding is consistent with earlier observations showing greater recruitment of inhibitory control in AU relative to AI rats, and may represent an adaptive adjustment in homeostatic control of excitatory/inhibitory balance, which exhibits a pronounced shift to overactivity in DG/CA3 in age-related memory impairment.

Disclosures: R.P. Haberman: None. **A. Monasterio:** None. **A.E. Branch:** None. **G. Blair:** None. **G. Rao:** None. **J.J. Knierim:** None. **M. Gallagher:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.21/RR7

Topic: H.01. Animal Cognition and Behavior

Support: NIA Grant AG09973

Title: Increased control of inhibitory/excitatory balance in aged rats with preserved memory function

Authors: *M. BRIDI[1], T. TRAN[1], M. KOH[2], M. GALLAGHER[2], A. KIRKWOOD[1]
[1]Zanvyl Krieger Mind/Brain Inst., [2]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: Recent studies in both rodent and humans identified that hyperactivity within the dentate gyrus-DG/CA3 region of the hippocampal formation is frequently observed in aged individuals as a potential contributing mechanism to the memory decline associated with aging and prodromal Alzheimer's disease (AD). It was of interest, therefore, to evaluate how age affects GABAergic inhibitory circuits in the DG. We did our studies in a rat model of aging (see companion presentations Haberman et al. and Bhammer et al.), in which each individual was behaviorally characterized as aged impaired (AI) or aged unimpaired (AU, with performance comparable to young individuals) in a standardized memory assessment. In hippocampal slices prepared from these individuals (AU, AI and Young) we studied the inhibitory inputs onto DG

granule cells using whole cell recordings. First, we quantified miniature inhibitory currents (mIPSCs), which provide a measure of the postsynaptic input strength, and found that the average mIPSC amplitude was larger in the AU than in the Young group, and that the smallest mIPSCs occurred in the AI group. Moreover, among the aged rats, the averaged mIPSC amplitude correlated positively with the individual's behavioral performance. We are currently evaluating the strength of distinct GABAergic circuits in the DG, and started with the powerful di-synaptic feedforward inhibition recruited by inputs from the lateral entorhinal cortex (LEC). To study this circuit in isolation we employed an optogenetic approach and virally expressed channelrhodopsin (ChR2) in the LEC. To quantify the strength of feedforward inhibition we computed the ratio of inhibitory and excitatory synaptic currents (I/E: recorded in granule cells under voltage clamp) evoked by optically stimulating LEC input. The results indicate a dramatic reduction of the I/E ratio in the AI group. We are currently using a similar approach for the inputs from the medial entorhinal cortex (MEC). In sum, our results thus far indicate that the preservation of memory function requires the functional integrity of circuits providing feedforward inhibition, and the potential upregulation of other yet to be identified circuits as an adaptive mechanism to preserve memory function.

Disclosures: M. Bridi: None. **T. Tran:** None. **M. Koh:** None. **M. Gallagher:** None. **A. Kirkwood:** None.

Poster

082. Learning and Memory: Aging, Circuits, and Molecules

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 082.22/RR8

Topic: H.01. Animal Cognition and Behavior

Support: Johns Hopkins University Science of Learning Award

Phyllis F. Albstein Fund for Research on Aging and Dementia

Title: Hippocampal CA3 miRNA and mRNA transcriptomes distinguish aged rats with impaired and preserved memory

Authors: *A. E. BRANCH[1], G. BLAIR[2], X. FU[3], M. GALLAGHER[4], J. M. BARABAN[2], R. P. HABERMAN[5]
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Abstract: As human longevity increases, there is a pressing need to develop strategies to avert the deterioration of cognitive abilities that is a common feature of aging. A priority of research in this field is therefore to identify age-related changes that may confer cognitive resilience, as well

as those which contribute to the onset and course of cognitive decline. Toward this goal, our lab makes use of a unique rodent model, aged outbred Long Evans rats, which exhibits a range of individual differences in outcomes including impaired and intact memory accompanied by neurobiological changes in underlying memory systems similar to observations in the aging human population. Our research program has obtained multiple microarray datasets in this model (Haberman et al., 2011; Haberman et al., 2013). Results from these studies revealed large complements of genes that differentiate aged rats with memory impairment (aged impaired, AI) from young adults (Y) and aged subjects that exhibit memory performance on par with young (aged unimpaired, AU). Differential expression profiles that reflect altered neural excitability and other underlying neurobiological changes are particularly pronounced in the CA3 hippocampal subfield. In our current work, we have used RNA-sequencing to profile both the mRNA and microRNA transcriptome of the CA3 subfield in an independent set of cognitively characterized young and aged rats to assess whether alterations in microRNA regulatory pathways may accompany observed changes in the mRNA transcriptome. mRNA expression differences determined by RNA-sequencing correlate well with basal mRNA profiles from our previous microarray analyses, confirming consistency of profiles across methodologies. Principle components analysis (PCA) of CA3 mRNA profiles show that mRNA expression clearly distinguishes between Y, AI, and AU rats. Intriguingly, PCA analysis of microRNA profiles most clearly separated subjects into cognitively intact (Y and AU) and cognitively impaired (AI) groups, suggesting that the microRNA transcriptome may be important for preserving memory in aging. Combined analyses of the two sequencing experiments show mRNA expression differences in the predicted target genes of microRNAs known to be involved in regulation of neuronal function including miR124 and miR138. Further investigation of these parallel data sets will allow identification of complementary changes in microRNA and mRNA systems that may promote preserved cognitive abilities over the course of aging, as well as identify those associated with cognitive decline.

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Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.01/RR9

Topic: H.01. Animal Cognition and Behavior

Support: ERC AdG 694539 SINCHAIS

Title: Ventro-dorsal hippocampal interaccion controls context memory formation

Authors: *F. FREDES, A. SILVA SIFUENTES, R. SHIGEMOTO
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Abstract: Places and emotions are tightly linked in our memories. In mammals, this link is indispensable for avoiding harmful environments and remembering beneficial ones. Dentate granule cells (GCs) in the dorsal hippocampus fire very sparsely when an animal enters to a novel environment; the activation of this small set of neurons induces emotional responses linked with a specific context memory. The classical view assumes that GCs firing is mainly driven by the excitatory input from the entorhinal cortex. However, it has been shown that the entorhinal cortex exerts only a weak influence on GCs firing, and hence on acquisition of context memory. Thus, the precise mechanisms by which GCs fire in order to form contextual memories are still unknown. We found that an intrahippocampal excitatory projection conveys a powerful drive over GCs in the dorsal dentate gyrus (DG). This projection, which originates from the mossy cells (MCs) located in the ventral portion of DG, targets the dendrites of dorsal GCs in the inner molecular layer. Electron microscopy confirmed that these terminals contact almost exclusively GCs spines. Using calcium imaging in freely behaving mice, we show that the activity of ventral MCs dramatically increases during novel environment exploration and decreases after familiarization. Local chemogenetic inhibition of ventral MCs terminals in the dorsal DG during the novel environment exploration significantly decreases the c-fos expression levels in dorsal GCs. Furthermore, the same manipulation in the acquisition phase of fear conditioning abolishes freezing during re-exposure to the same environment, whereas it has no effects on freezing levels in the retrieval phase. Thus, our results suggest that a previously overlooked ventro-dorsal hippocampal interaction is required for the firing of dorsal GCs and consequently, context memory acquisition, challenging the classical view of the hippocampal contextual memory formation.

Disclosures: F. Fredes: None. **A. Silva Sifuentes:** None. **R. Shigemoto:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

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Program#/Poster#: 083.02/RR10

Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI JP15J05936

Title: Reactivation of neuronal subpopulation in the dentate gyrus during memory recalls with long intervals

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Abstract: In the hippocampus, the dentate gyrus (DG) is crucial for encoding spatial and contextual memory in rodents. Based on lesion studies, it is widely accepted that the hippocampus becomes dispensable for memory recall progressively over time. However, it remains unknown whether the hippocampus is involved in remote memory recall processes under undisturbed conditions. In this study, we sought to evaluate the possible role of hippocampal activity in remote memory recall by using a novel cell labeling system in mice. Immediate early genes, such as *Arc*, are transiently induced by physiological synaptic activity in neurons and have therefore been considered reliable markers for activated neurons. Here, we established a double transgenic mouse line to independently label cell ensembles activated during two different events with two fluorescent proteins of different colors. In this system, a 4-hydroxytamoxifen (4-OHT)-controllable flippase (FLP) recombinase and a destabilized yellow fluorescent protein Venus-PEST were expressed under the control of the *Arc* promoter in one transgene, and teal fluorescent protein (mTFP1) was constitutively expressed upon FLP-mediated recombination in the other transgene. Thus, activated cells were transiently labeled with Venus-pest and persistently labeled with mTFP1 after 4-OHT administration. We first trained mice in a contextual fear-conditioning paradigm and mTFP1 labeled neurons that were activated during the recall of fearful memories 24 h after the training period. When the mice underwent the second recall period 4 days after the first recall event, we found that a subpopulation of neurons in the DG was double-labeled with mTFP1 and Venus-PEST, approximately three-fold above the theoretical level of chance. Surprisingly, when the interval between the two recall events was extended to a month, a similar number of double-labeled cells were observed in the DG, indicating repeated activation across the recent and remote recalls. These findings suggest that a subpopulation of hippocampal DG neurons is reactivated by memory recall, even with a long interval after memory acquisition, and raise a possibility that the hippocampus plays a role in the context processing of remote memory and contributes to remote memory recall.

Disclosures: A. Araki: None. **K. Minatohara:** None. **M. Akiyoshi:** None. **I. Imayoshi:** None. **R. Kim:** None. **T. Kawashima:** None. **H. Bito:** None. **R. Kageyama:** None. **H. Okuno:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.03/RR11

Topic: H.01. Animal Cognition and Behavior

Support: UW-Madison Institute for Clinical and Translational Research

Title: Exploration of noisy synaptic dynamics as a potential mechanism for temporal pattern separation in the dentate gyrus

Authors: A. MADAR[1], L. A. EWELL[2], J. A. PFAMMATTER[3], *M. V. JONES[4]
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Abstract: Pattern separation is the neuronal computation supposed to support our ability to store similar experiences as distinct memory traces. The dentate gyrus (DG) of the hippocampus is generally thought to perform this process, transforming similar cortical input patterns into dissimilar output patterns before they are transferred and stored in CA3. Despite the centrality of this 30-year old hypothesis to most theories of episodic memory, whether the DG network per se reduces the overlap between similar inputs, and how it performs this computation remains a mystery. Using the ability to directly control input stimuli and to measure outputs afforded by slice electrophysiology, we recently showed that the isolated DG circuitry decorrelates input spiketrains at the level of single neurons[1]. This decorrelation cannot be explained by simple noisy transmission that would randomly fail to produce an output spike or add a random jitter. However, we discovered a strong relationship between trial-to-trial variability and pattern decorrelation. Yet, averaging out this variability shows that it is not the only source of decorrelation. We hypothesize that probabilistic synaptic short-term dynamics at different classes of synapses in the DG network are responsible for allowing granule cells (GCs) to balance strong decorrelation with sufficiently reliable information transmission. To test this, we are assessing the synaptic facilitation and depression in GCs (whole-cell voltage-clamp) in response to the same Poisson spiketrains used in our pattern separation experiments[2], in adult mice with or without temporal lobe epilepsy. We will use these data to constrain computational network models with dynamic synapses in order to investigate the impact of different synapses (e.g. Perforant path to GC or fast-spiking interneurons (FS), FS to GC, etc) on temporal pattern separation.
References:
[1]: Madar, Ewell & Jones. (2017) Pattern separation of spiketrains by individual granule cells of the dentate gyrus. *bioRxiv*, doi:10.1101/107706
[2]: Tsodyks, Pawelzik & Markram (1998) Neural networks with dynamic synapses. *Neural computation* 10, 821-835

Disclosures: A. Madar: None. **L.A. Ewell:** None. **J.A. Pfammatter:** None. **M.V. Jones:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.04/RR12

Topic: H.01. Animal Cognition and Behavior

Title: High ω3-polyunsaturated fatty acids in fat-1 mice prevent scopolamine-induced granular cell degeneration through BDNF signaling

Authors: *H. TAE WOONG[1], D. GWON[1], S.-A. SHIN[2], J. SHIN[2], J. HONG[2], K. LIM[2], M. MOON[3], J. RO[4], J.-J. KIM[2], D. KIM[2]
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Abstract: ω-3 polyunsaturated fatty acids (PUFAs) are known to be critical for optimal brain health and psychiatric and neurological ailments. We have shown the effects of scopolamine on memory impairment in the omega-3 overexpressed fat-1 mouse hippocampus. Fat-1 mice were given doses of scopolamine and Y-maze and passive avoidance tests were performed to evaluate the mice's memory function. Fat-1 mice showed increased latency in the passive avoidance test and improved ameliorated alternation in y-maze. The effects of scopolamine on damaged hippocampal neurogenesis was confirmed by the increase of ki-67 and DCX positive stained cells in the fat-1 mice. Western blot analysis revealed that expression of brain-derived neurotrophic factor (BDNF) and phosphorylated cAMP response element-binding proteins (pCREB) was increased. We were able to confirm that omega-3 was effective for scopolamine-induced apoptosis by using the cleaved-Caspase 3 Western Blot. In conclusion, these findings indicate that scopolamine-treated fat-1 mice were protected from granular cell loss and exhibited increased BDNF signaling and decreased apoptosis signaling. These processes may underlie granular cell survival and maybe provide potential therapeutic targets for treatment of memory impairment.

Disclosures: H. Tae Woong: None. **D. Gwon:** None. **S. Shin:** None. **J. Shin:** None. **J. Hong:** None. **K. Lim:** None. **M. Moon:** None. **J. Ro:** None. **J. Kim:** None. **D. Kim:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

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Program#/Poster#: 083.05/RR13

Topic: H.01. Animal Cognition and Behavior

Support: NSERC Discovery Grant 402642

NSERC Discovery Grant 402651

Title: Contribution of the ventral dentate gyrus to learned approach avoidance conflict processing

Authors: D. C. M. YEATES, A. C. H. LEE, *R. ITO
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Abstract: Manipulations (lesions, inhibition, etc) of the ventral hippocampus (vHPC) lead to reductions in innate and conditioned fear, anxiety, and social behaviours. It has been suggested that these effects arise due to the fact that the vHPC ordinarily detects and resolves approach-avoidance conflict scenarios, in which an animal must either decide to approach or avoid ambivalent stimuli imbued with both positive and negative valences. Presently, little research has explored the contributions of the vHPC subfields to approach-avoidance conflict resolution, with only a few studies looking at the role of the vHPC subfields in general affective processes. This study extends recent work from our laboratory showing a dissociation in the control of learned approach avoidance conflict behaviour between the ventral CA3 and CA1 subfields, by focusing on the role of the ventral dentate gyrus (vDG) in learned approach-avoidance conflict processing. Male Long-Evans rats were trained to associate 3 visuotactile cues with reward, punishment, or no outcome over 12 sessions in a 3-arm maze. Upon successful acquisition of the cue-outcome associations, rats received bilateral infusions of either GABAR agonists baclofen /muscimol, or saline into their ventral or dorsal DG. They then underwent a 'conflict test' in which they were free to explore a 2-arm maze with the presentation of a combined positive-negative cue in one arm and a neutral cue in the other arm. Preliminary data suggest that GABAR-mediated inhibition of the vDG increased approach tendency in the face of motivational conflict, akin to the effects we previously observed with GABAR agonism of the ventral CA3 subfield. These findings indicate that under normal circumstances, the ventral DG and CA3 subfields may work co-operatively to oppose approach behaviour (or facilitate avoidance) in the face of a motivational conflict, whereas the CA1 subfield may act independently from the vCA3 and vDG to encourage approach tendencies in conflict scenarios.

Disclosures: D.C.M. Yeates: None. **A.C.H. Lee:** None. **R. Ito:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.06/RR14

Topic: H.01. Animal Cognition and Behavior

Title: Activation of the supramammillary nucleus-dentate gyrus pathway by optogenetic induces an increase in theta and gamma power

Authors: *P.-H. LUPPI[1], F. BILLWILLER[1], M. ESCLAPEZ[2]
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Abstract: Recent studies strongly support a role of the two states of sleep, slow wave (SWS) and paradoxical sleep (PS) in learning and memory consolidation. However, the mechanisms underlying the beneficial effect of both states of sleep in learning and memory have not yet been identified. To this aim, we recently identified at cellular level the populations of cortical neurons activated and displaying plasticity during PS hypersomnia by means of functional neuroanatomy. Such mapping clearly showed for the first time that only a small number of limbic structures are activated during PS in contrast to waking. Among them, the dentate gyrus (DG) is the only cortical region that display more activated neurons during PS hypersomnia than during waking (Renouard et al., 2015). Further, combining retrograde tracing, neurotoxic lesion and FOS immunostaining, we showed that neurons from the lateral part of the supramammillary nucleus (SuML) projecting to the DG, are responsible for the activation of DG granule cells during PS. These surprising results pointed out for the first time that the SuML/DG pathway activates DG granule cells specifically during PS. To further study this pathway, we transfected channelrhodopsin or Halorhodopsin in the glutamatergic neurons of the SumL in vGlut2Cre mice using Cre dependent AAVs. Control vGLUT2-Cre mice received the viral vector containing only the fluorescent reporter EYFP. Mice were implanted with EEG and EMG electrodes and a custom made optrode was placed unilaterally in the dorsal DG. Optical stimulations were applied at 20hz during 10s during waking, SWS and PS. The last day, the mice were stimulated 15 min and perfused 90 min later. Optogenetic stimulation during SWS but not PS induced waking in ChR2 but not in control mice. Optogenetic stimulations during SWS and waking induced an increase in muscle activity only in ChR2 mice. Stimulations during the three states induced a significant increase in the theta/delta power ratio and in gamma power in the DG LFP. Stimulations during PS induced an increase of the theta peak frequency. Stimulation before perfusion induced a strong and significant increase in the number of Fos-labeled neurons in the DG region ventral to optic fiber only in ChR2mice. Inhibition of DG fibers in mice using halorhodopsin induced no effect on the state of the animal nor on the LFP. Our results indicate that the SumL/DG pathway increases theta power and frequency. Since our previous results indicate that the pathway is mainly active during PS, it suggests that it would be responsible for the increase in theta and gamma power occurring specifically in the DG during PS reported previously (Montgomery et al., 2008).

Disclosures: **P. Luppi:** None. **F. Billwiller:** None. **M. Esclapez:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

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IDEX Unistra

Title: Increased theta gamma coupling within dentate networks during the planning stage of spatial navigation

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Abstract: Spatial navigation often relies on the ability to retrieve in advance a representation of the desired location. The hippocampal formation, important for spatial learning and memory, is expected to be crucially involved in prospective coding and the planning of trajectories towards the goal position. Hence, this network should be particularly active in place navigation strategies relying on a cognitive map to plan the future path. To test this hypothesis, we recorded the local field potentials (LFPs) in the dorsal dentate gyrus (DG) and CA1 regions of mice during a novel reference memory task based on an 8-arm radial maze. In this task, the mice must reach the end of a fixed reward arm from a different, pseudo-random starting arm. Across ten days of training, mice usually switch from random to serial and then place strategy of navigation. Preliminary results (n=3 mice) suggest a learning-dependent, transient increase in theta (4-12 Hz)-gamma (60-100 Hz) phase-amplitude coupling occurring especially before committing to the rewarded arm. This is reminiscent of the increased dentate theta-gamma coupling we observed previously during the approach to the rewarded location in a modified Barnes maze task (Bott et al., 2016). Interestingly, this theta-gamma coupling was differentially modulated by the navigational strategy and between the different hippocampal structures. Relatively constant in CA1 within trials and across days/strategies, the coupling is more prominent during a place navigation strategy in the DG molecular layer, which is strongly innervated by the entorhinal cortex (EC). As theta-gamma coupling participates to some mnesic processes and information transfer by allowing a tight synchrony between areas, it is well-positioned to mediate the transfer of information necessary for route planning. Simultaneous LFP recording in the DG, CA1 and medial EC in other mice (n=3) during the above task supports this view as a similar, coincident pattern of coupling activity was highlighted in both the DG and the EC. Overall, we propose that

the entorhinal-DG network might use a theta-gamma neural code to plan future trajectories during place navigation.

Disclosures: V. Douchamps: None. **D. Kerspern:** None. **C. Mathis:** None. **R. Goutagny:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

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Title: Stimulation of c-fos activity by IEG-promoting phenolic metabolites modulates optogenetic recapitulation of learned behavior

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Abstract: Chronic sleep deprivation (SD), a common problem in our society, is linked to a number of physiological and cognitive co-morbidities, including heart disease, high blood pressure, mental illness, and memory deficits. Recent studies indicate that SD disrupts the consolidation period of memory formation through downregulation of the cAMP/PKA/CREB signaling pathway, mTOR signaling, and decreased expression of plasticity-related genes, including immediate early genes (IEGs) such as c-fos. We have found that treatment with a Bioactive Dietary Polyphenol Preparation (BDPP) and microbiome-derived phenolic metabolites confers physiological resilience against SD-induced cognitive deficits, activates the CamKII/CREB and mTOR signaling pathways, and induces IEG expression in live animals and cortico-hippocampal neurons. To determine the mechanisms through which phenolic metabolites confer resilience to SD in memory-bearing neurons, we will use a novel c-fos-tTA/TRE-ChR2-mCherry optogenetics system in which transgenic mice are injected with AAV9-TRE-ChR2-mCherry in the dentate gyrus to allow training-induced expression of ChR2-mCherry in activated neurons (TetTagging). This system has previously been used to generate false memories and has been used by our lab to recapitulate learned behavior in the contextual fear conditioning (CFC) memory test. To examine pathways modulated by BDPP and phenolic metabolites, mice are pretreated prior to testing, habituated in Context A to record basal freezing, then fear conditioned in Context B to label a subpopulation of c-fos-expressing neurons with ChR2-mCherry. Mice are then reintroduced to Context A under photostimulation to record recapitulation of learned fear

behavior in an unrelated context. Modulation of c-fos activity by treatment will result in increased expression of ChR2-mCherry in the hippocampus and light-induced freezing upon activation of memory-bearing neurons, allowing for quantification of treatment-induced resilience to SD. Histological studies will examine the overlap of neurons co-expressing ChR2 and c-fos, as well as CREB and other plasticity-related signaling pathways to determine mechanistically how IEG-inducing metabolites confer resilience to SD in memory-bearing neurons. Through TetTagging of specific populations of neurons, we will examine individual neuronal responses to therapy and the responses of brain regions to optogenetic modulation. Due to the prevalence of SD in our society, an understanding of the mechanisms through which SD induces cognitive deficits is of great importance.

Disclosures: C. Smith: None. **J. Brathwaite:** None. **T. Frolinger:** None. **J. Wang:** None. **G.M. Pasinetti:** None.

Poster

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Title: Dentate gyrus contributes to retrieval as well as encoding: Evidence from context fear conditioning, recall and extinction

Authors: *B. E. BERNIER[1], A. F. LACAGNINA[2], A. AYOUB[3], F. SHUE[3], B. V. ZEMELMAN[3], F. B. KRASNE[4], M. R. DREW[5]
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Abstract: Dentate gyrus (DG) is widely thought to provide a teaching signal that enables hippocampal encoding of memories, but its role during retrieval is poorly understood. Some data

and models suggest that DG plays no role in retrieval; others encourage the opposite conclusion. To resolve this controversy, we evaluated the effects of optogenetic inhibition of dorsal DG during context fear conditioning, recall, generalization, and extinction in male mice. We found that (1) inhibition during training impaired context fear acquisition; (2) inhibition during recall did not impair fear expression in the training context, unless mice had to distinguish between similar feared and neutral contexts; (3) inhibition increased generalization of fear to an unfamiliar context that was similar to a feared one and impaired fear expression in the conditioned context when it was similar to a neutral one; (4) inhibition impaired fear extinction. These effects, as well as several seemingly contradictory published findings, could be reproduced by BACON, a physiologically realistic hippocampal model positing that acquisition and retrieval both involve coordinated activity in DG and CA3. Our findings thus suggest that DG contributes to retrieval and extinction, as well as to the initial establishment of context fear.

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Poster

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Title: Identification and manipulation of fear extinction engrams in the hippocampus

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Abstract: Fear extinction is a form of exposure therapy in which repeated presentations of a fearful stimulus in the absence of threat gradually reduce fear. Instead of erasing the original memory, extinction appears to create a parallel memory trace that inhibits or competes with the original memory. Acquisition of extinction learning is believed to involve plasticity in amygdala and prefrontal cortex, but the mechanisms controlling retrieval of extinction are not well understood. Based on recent evidence that activity of granule cell ensembles in the dentate gyrus

(DG) is necessary and sufficient for recall of contextual fear memories, we assessed the role of these cells in acquisition and recall of contextual fear extinction. We utilized ArcCreER^{T2} transgenic mice to indelibly tag and manipulate granule cells active during contextual fear acquisition or extinction. When fear acquisition cells were tagged, their probability of reactivation during re-exposure to the training context was reduced after extinction training. Extinction training did not, however, reduce the overall number of cells acutely activated by context re-exposure, suggesting that extinction activates an ensemble that is distinct from the fear acquisition ensemble. To test the hypothesis that the acquisition and extinction activate unique ensembles, we used the ArcCreER^{T2} system to express halorhodopsin in neurons active during either fear acquisition or extinction. Silencing extinction cells in the DG increased fear during a test of extinction retrieval, but had no effect during a spontaneous recovery test one month after extinction. Conversely, silencing fear acquisition cells in the DG had no effect during a test of extinction retrieval but reduced fear during the spontaneous recovery test one month later. The behavioral effects of silencing either population were specific to the conditioned context, suggesting that the manipulations modulate expression of specific contextual memories rather than general emotional states. Our findings suggest that contextual fear acquisition and extinction memories are coded by unique neural ensembles in the DG. Activity of fear acquisition cells is required for expression of spontaneous recovery, whereas activity of extinction cells is required for expression of fear extinction. We hypothesize that expression of fear versus extinction memories is determined by competition between ensembles in the hippocampus.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Title: Correlation between neurogenesis in the hippocampus and behavior test in Wistar Kyoto rat

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Abstract: [Objective] Depression is one of the most common diseases and a burdensome health problem. The hippocampus is thought to be an important region for depression. However, the relationship between hippocampal neurogenesis and depression is still controversial. Wistar Kyoto (WKY) rats are frequently used as a depression model. The neurogenesis of WKY rats is still unidentified. We first evaluated the neurogenesis of WKY rats and compared it to that of Wistar (WIS) rats. [Materials and Methods] We used age-matched adult male WKY and WIS rats (5 to 7 weeks old at the beginning of the experiment, n = 30). Each strain was divided into two groups, a behavior test group (n = 20) and a control group (n = 10). We performed sucrose preference test (SPT), open field test (OFT) and forced swim test (FST) in the behavior test group. In order to evaluate the endogenous neurogenesis in the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus, the proliferative cells that incorporated 5-bromo-2'-deoxyuridine (BrdU) were counted. BrdU was administered to both groups of rats at a concentration of 50 mg/kg body weight, with five consecutive intraperitoneal injections every 12 h from last 3 days. [Results and Discussion] No strain effect was observed in the number of cells positive for BrdU and BrdU/Doublecortin (Dcx) in the SVZ. However, the number of BrdU- and BrdU/Dcx-positive cells in the DG of the hippocampus was significantly lower in WKY rats than in WIS rats. Behavior tests did not affect neurogenesis in either strain. Hippocampal neurogenesis correlated negatively with the results of a forced swim test (FST) on day 2 in each strain. That is, as the rats that neurogenesis in the DG have decreased, immobile time of the FST day2 was in a long trend. [Conclusion] Our findings indicate that native cell proliferation and neurogenesis in the DG are correlated with stress resistance. Neurogenesis in the DG may be an etiological factor for depression, and has the potential to be a new target for depression treatment.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01NS054281

Title: Interneuronal postinhibitory rebound can mediate gamma oscillations in pyramidal-interneuronal network

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Abstract: Gamma oscillations are believed to play a critical role in information processing, encoding, and retrieval. Gamma rhythms do not all have the same characteristics and may have distinct underlying mechanisms. For example, pyramidal neurons in area CA3 were strongly modulated by an in vitro gamma rhythm, whereas in CA1 they were only weakly modulated (Zemankovics et al. J. Neurosci. 33:12337, 2013). Inhibitory interneuronal network gamma (ING) and pyramidal-interneuronal network gamma (PING) oscillations may arise from a coupled oscillator mechanism in which individual neurons oscillate, or from a population oscillator in which individual neurons fire sparsely and stochastically. Recently, a third mechanism called PIR-ING was proposed (Tikidji-Hamburyan et. al. J. Neurosci. 35:15682, 2015) that requires interneurons with type 2 excitability that exhibit postinhibitory rebound (PIR). The rebound latency is fairly constant, and together with the synaptic delay sets the period of the population rhythm. This mechanism has advantages over other ING models such as robustness to noise and heterogeneity (in contrast to coupled type 1 oscillator models) and the ability to combine tight synchrony with interneurons participating in a large fraction of the population cycles (in contrast to stochastic population models). In this study, we extend the PIR-based mechanism from a network that includes only interneurons (I-cells) to one with 1120 type 1 excitatory (E) neurons and 280 type 2 inhibitory (I) neurons. The sparsely-connected network of conductance-based, single-compartment neurons was implemented in the simulation package NEURON. E-cells are driven by random external synaptic inputs (g_{EXT}) and provide excitatory inputs to inhibitory population (g_{EI}). We varied the strength of the excitation of the I-cells by the E-cells (g_{EI}), as well as g_{EXT}. For low values of (g_{EXT}) but high values of (g_{EI}), a PIR-PING mechanism is observed in which the PIR latency set the period, E-cells population rate is only weakly modulated, and individual E-cell firing rate is low. For lower values of g_{IE} and higher g_{EXT} that together increase the E-cell rate, a classical coupled oscillator PING mechanism is observed. The period is shorter than in PIR-ING because the excitation received becomes sufficient to cause I-cell firing directly, rather than relying on PIR; the recovery from inhibition in the E-cells then sets the period. These different gamma mechanisms (PIR-PING and coupled oscillator PING) may underlie distinct types of gamma synchrony that have been observed experimentally.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: ES100221

T32-NS007431

Title: Hippocampal oscillatory networks and chemogenetic manipulation of area CA2

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Abstract: Hippocampal area CA2 is a distinct sub-region embedded in the neural circuits known to underlie long term memory. CA2 receives input from the hypothalamus and exhibits high expression levels of vasopressin 1b and oxytocin receptors which, together, are highly suggestive of a specialized role for CA2 in social memory. Despite evidence that CA2 pyramidal cell transmission is required for intact social memory, little is known about how CA2 affects the flow of information in larger intra-hippocampal circuits during active, awake behaviors. Neural oscillations represent the synchronous activity of large groups of neurons and their presence in the hippocampus has been correlated with learning, yet few studies have investigated these oscillations in the context of social behavior, or have established causation between oscillations and behavior. Given CA2's role as a socio-cognitive memory hub, we investigated how CA2 oscillatory networks are organized during social behavior, and how that structure may affect the flow of information in hippocampal circuits. To begin to address the relationship between CA2 neuronal activity and hippocampal oscillations, we infused adeno-associated viruses coding for a cre-dependent inhibitory DREADD (hM4Di) into hippocampi of mice that express cre recombinase selectively in CA2 pyramidal cells under the control of the *Amigo2* promoter (Amigo2icreERT mice). We then implanted electrode arrays to monitor activity of hippocampal oscillations before and following administration of the DREADD ligand, Clozapine-N-oxide (CNO), while animals were allowed to freely explore a clean home cage that was either empty, contained a social stimulus, or contained a non-social stimulus. We found in hM4Di-infused Amigo2icreERT mice CNO decreased neuronal activity in the gamma frequency range (25-90Hz) in CA1 stratum pyramidal during periods of mobility when no stimulus was present, suggesting that CA2 contributes to the organization of gamma oscillatory activity in CA1 during spatial exploration. During investigation of a novel social stimulus, we observed increased power in the beta frequency range (15-25Hz) in one of CA2's synaptic target areas, CA1 stratum oriens. When CNO was present; however, this shift in beta band power was eliminated, suggesting a mechanism by which CA2 could contribute to the organization of oscillatory activity during encoding of social information. Together these findings suggest that CA2 plays a role in organizing hippocampal network activity during both spatial and social processing, and it does so in a layer- and frequency-specific manner.

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Poster

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Title: Impaired *In vivo* gamma oscillations in the medial entorhinal cortex of knock-in Alzheimer model

Authors: *T. NAKAZONO[1,2], T. N. LAM[1,2], A. Y. PATEL[1,2], M. KITAZAWA[3], T. SAITO[4], T. C. SAIDO[4], K. M. IGARASHI[1,5,2]
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Abstract: Alzheimer's disease (AD) is one of the most common form of dementia. For successful therapy of AD, we need to identify what types of neural circuit activity are affected and how impairments in circuit function progress in AD. The entorhinal cortex receives input from multiple cortical regions and sends bidirectional projections to the hippocampus. This circuit is deeply involved in the formation of new memories and is suggested to be a primary site of dysfunction in AD. However, it is unknown what type of circuit activities are affected in AD. We investigated how circuit activities are affected in the entorhinal cortex of AD mouse model. We used APP knock-in AD model mice (Saito et al., Nat Neurosci 2014) and recorded in vivo spontaneous neuronal activities and local field potentials from entorhinal cortex of anesthetized young mice (5 months old). Cross-frequency coupling of gamma (30-100 Hz) oscillations to theta oscillations was reduced in APP knock-in mice. Phase locking of spiking activity of layer II/III pyramidal cells to the gamma oscillations was significantly impaired. These data indicate that the neural circuit activities organized by gamma oscillations were disrupted in the entorhinal cortex of AD mouse model, and point to gamma oscillations as one of possible mechanisms for cognitive dysfunction in AD patients.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: R01MH065658

Title: Modulation of hippocampal-prefrontal oscillations in Shank3 rats through fimbria-fornix stimulation

Authors: *V. LUO, M. L. SHAPIRO
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Abstract: Many neuropsychiatric and neurodevelopmental disorders are associated with fronto-temporal dysfunction, yet the mechanisms that support communication between these distributed networks are largely unknown. Synchrony of neural oscillations accompanies effective signaling and communication between brain regions, and impaired interactions between the hippocampus and the prefrontal cortex (PFC) are accompanied by abnormal oscillations in schizophrenia and autism spectrum disorder (ASD). Deep brain stimulation (DBS) can modulate local field potentials (LFPs), and fimbria-fornix (FFx) stimulation that increased theta-gamma power comodulation of hippocampal LFPs predicted improved cognition and memory performance in otherwise amnestic rats. We hypothesize that specific DBS parameters modulate oscillations across structures and determine their functional effects. We tested this hypothesis by varying the magnitude and temporal pattern of electrical stimulation of the FFx in behaving rats while recording simultaneously in the medial PFC and the dorsal and ventral CA1. Preliminary results show that theta-burst stimulation of the FFx altered the amplitude and phase of theta LFPs (4-12 Hz) by increasing the synchrony and reducing the phase differences of theta across all three recording sites. Compared to wild-type rats, Shank3 heterozygous rats CA1 had reduced endogenous theta power and heightened sensitivity to FFx stimulation. Future experiments will determine how different DBS parameters alter cognitive performance in memory tasks.

Disclosures: V. Luo: None. **M.L. Shapiro:** None.

Poster

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Support: SPS KAKENHI 17K16365

Title: Decoding subsequent behavioral response to tone stimulus from rat hippocampal local field potential recordings using deep learning

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Abstract: Local field potential (LFP) recordings and electroencephalogram recordings (EEG) are thought to reflect coherent activities of the local multiple neurons. Those recordings are easily acquired than single unit recordings, and often are less invasive. Thus, it is of importance to what extent we can decode the information such as the neural representation of external stimuli, ongoing and subsequent behavior, or some pathological symptoms, from those recordings. On the other hand, recent advancement in the field of machine learning achieved remarkable performance in pattern recognition. Especially, it is now possible by deep learning to extract unknown low dimensional representation characterizing the given data, without handcrafting features. However, even though deep learning is extensively studied in image recognition, the reports of utilizing deep learning algorithm to LFP of EEG recordings are limited. In this study, we examined whether deep learning algorithm is able to predict rat's behavioral response to tone stimulus from the hippocampal LFP. The data is from previous study (Tokuda et al, PloS One, 2014). Five rats underwent serial feature positive conditional discrimination task in eyeblink conditioning. Each rat underwent daily session, which consists of 100 trials, and lasted about 30 minutes. During each session, continuous recording of dorsal hippocampal LFP was conducted. Firstly, all of the data from all the rats were used to pre-train Stacked Auto Encoders (SAE). Then, fine-tuning was conducted with 2-seconds long segments immediately preceding the onset of the tone stimulus as the input to let the network predict the behavioral response of the rat. Leave-one-rat-out cross validation resulted in significant ability of the network to predict the behavior (average accuracy >70%). This suggested that the algorithm could extract the feature in the LFP that has the information to predict the subsequent behavior, from recordings of four rats. When all of the trials over all sessions of all rats were randomly divided into training data and test data, the network could predict correct behavioral response in all trials in both training data and test data. This suggests that SAE could perform subject-

specific prediction with very high accuracy, where the specific recording from the specific electrode can be incorporated within the training data.

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Poster

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Title: In the medial prefrontal cortex gamma couples to respiration, not theta

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Abstract: Theta (4-12 Hz) and gamma (30-160 Hz) oscillations are prevalent in local field potential (LFP) recordings from many brain regions. These rhythms not only co-exist but often interact by phase-amplitude coupling, in which the theta phase modulates the amplitude of gamma. Since theta tends to be coherent over long distances, it is usually thought as a global slow rhythm aiding cross-regional communication. Theta-gamma coupling would then constitute a mechanism for linking distributed gamma assemblies. However, in this work we show evidence that points towards an alternative global brain rhythm: respiration-entrained LFP oscillations, which phase-lock to nasal breathing cycles. Respiration-locked oscillations are particularly prominent in the medial prefrontal cortex (mPFC), where they modulate gamma activity. In fact, new results suggest that gamma exclusively couples to respiration in the mPFC, without stable phase relationship to theta which can be present at the same time. In small rodents, respiration-entrained LFP rhythms may occur at theta frequency. We therefore caution that previous studies on theta power, cross-regional theta synchrony, and theta-gamma coupling may have instead detected the respiration-locked LFP rhythm and respiration-gamma coupling. Interestingly, two physiological features separate the slow oscillations: (1) the gamma sub-band modulated by respiration differs from the gamma sub-bands modulated by theta, and (2) during

REM sleep, respiration-gamma coupling decreases while theta-gamma coupling increases. Nevertheless, without simultaneously tracking nasal respiration, we argue that it may be difficult to distinguish between theta and respiration-entrained LFP rhythms.

Disclosures: **A.B. Tort:** None. **J. Brankačk:** None. **A. Draguhn:** None.

Poster

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Title: Coding for interactive behaviors of medial prefrontal areas during joint operant conditioning in male rats

Authors: *A. GRUART[1], A. R. CONDE-MORO[1], F. DA ROCHA-ALMEIDA[1], R. SANCHEZ-CAMPUSANO[2], J. DELGADO-GARCIA[3]
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Abstract: Brains of social animals are continuously exchanging information and coordinating interdependent behaviors with their conspecifics. These interactions provide them with better adaptive strategies. Although there have been reported different attempts to reproduce interactive behaviors in the laboratory context, the majority of them have been focused on the behavioral level. The main objective of this study was to identify the activity of medial prefrontal circuits present when animals have to work together in order to obtain a common reward. For this aim, we developed a behavioral procedure to reproduce these behaviors in two customized adjacent Skinner boxes that were divided by a metallic grid. The experimental boxes were configured in a way that two male rats could see and smell each other and also have limited physical contact through the grid. Rats were progressively trained to climb at the same time (and stay simultaneously for 2-4 s) on a platform in order to get food pellets for both of them. It took 4-5 days for them to learn to climb individually on the platform and another 5-6 days to do it simultaneously. This set up was also compatible with the *in vivo* electrophysiological recording of local field potentials (LFPs) throughout the task. Electrodes were implanted in the medial prefrontal cortex (mPFC) of all rats as these areas have been previously related with cooperative behaviors in humans and non-human primates. LFPs were recorded from five pairs of rats across the whole conditioning procedure. Preliminary results of the recorded LFPs indicate the selective involvement of the mPFC during interactive behaviors in rats, showing differences in the spectral power when the rats climbed on the platform individually as opposite to when they climbed

simultaneously. A detailed analysis of recorded LFPs indicated a progressive increase in power for delta and theta bands during the acquisition process. In particular, this dominant delta activity seemed to concentrate during the period in which rats were located on the platform. Importantly, the spectral power was even larger when rats have to stay together on the platform than when they jump individually on it. In addition, when paired together rats presented significant differences in the power of delta and theta bands depending on their condition of leader or of follower of the joint activity. In summary, mPFC cortex seems to encode neural commands related to the individual and joint acquisition of an operant conditioning task by behaving rats.

Disclosures: A. Gruart: None. **A.R. Conde-Moro:** None. **F. da Rocha-Almeida:** None. **R. Sanchez-Campusano:** None. **J. Delgado-Garcia:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.19/RR27

Topic: H.01. Animal Cognition and Behavior

Support: FIS/IMSS/PROT/G15/1458

Title: Differences in eeg power and coherence between young and elderly healthy adults during an incidental/ intentional learning/memory visuospatial task

Authors: M. JUNCO[1], O. MEJÍA-RODRÍGUEZ[2], M. CERVANTES[3], M. A. LÓPEZ-VÁZQUEZ[2], *M. OLVERA-CORTES[2]
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Abstract: The question about the participation of the same cerebral structures and similar neural processes in encoding both episodic and incidental information along the life is not actually answered. Ageing process appears to affect earlier the incidental encoding and the deficiencies are qualitatively different for incidental or intentional encoding, in support of differential processing of incidental versus intentional encoding/recall. The EEG recorded during the emission of correct responses (recall) in an incidental/intentional visuospatial task in fronto-temporal derivations from young (25-40 years old), and elderly (60-85 years old) healthy volunteers was analyzed. Power and coherence between regions were obtained from 4 seconds EEG samples encompassing the decision (old items correctly recognized and new items correctly rejected) and were compared between groups in four conditions: baseline (open eyes), incidental 1 (small load), incidental 2 (high load) and intentional recovery. Higher power in the theta band

(4-8 Hz) and gamma band (30-45 Hz) was observed in the elderly adults in frontal and temporal derivations (Fp1, Fp2, F3, F4, F7, F8, T4, T5 and T6). Left intra-hemispheric, and inter-hemispheric F3-F4, F7-F8 and T3-T4 coherences were lower for elderly participants in the theta band. No differences between incidental and intentional recall were observed in any group. The EEG related to the recall of correct information changes with the age, without respect of the acquisition process (incidental/intentional). The only derivation without differences in power and coherence was T3, possibly related to the efficiency of recall. It was hypothesized that incidental learning is occurring during the recall process rather than during the first exposition to the information (since no effort to memorize occur), however the present results don't show differences between incidental and intentional successful recall. The differences observed in the present work are most probably related to aging, but not with efficiency of processing of visuospatial information.

Disclosures: M. Junco: None. **O. Mejía-Rodríguez:** None. **M. Cervantes:** None. **M.A. López-Vázquez:** None. **M. Olvera-Cortes:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

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Program#/Poster#: 083.20/RR28

Topic: H.01. Animal Cognition and Behavior

Support: NINDS R01-NS078396

NSF BCS-1358907

NIH 5T32GM008412- 20

NSF GRFP

Title: Oscillatory states in human parietal cortex predict subsequent memory performance: Evidence from ECoG recordings

Authors: *A. GONZALEZ[1], J. B. HUTCHINSON[4], M. R. UNCAPHER[5], J. PARVIZI[2], A. D. WAGNER[3]
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Abstract: Neural oscillatory activity, at theta and alpha frequencies, is linked to multiple cognitive phenomena. Decreases in stimulus-evoked posterior cortical alpha power (8-12Hz) are thought to indicate greater attentional control, and have been shown to predict performance on multiple tasks. Within the context of memory, increases in stimulus-evoked theta power (4-8Hz)

track better encoding, as indexed by later memory performance. In addition to stimulus-evoked effects, oscillations could also represent neural states that affect how incoming stimuli are subsequently processed. To investigate this possibility, we examined pre-stimulus activity during the encoding phase of an episodic memory task in 8 ECoG patients with lateral parietal cortical coverage. Subjects made semantic (abstract/concrete) decisions on words (encoding phase), followed by old/new recognition memory decisions that required discriminating studied from novel stimuli. For both phases, we used reaction times (RTs) as the measure of interest to examine the relation to oscillatory power around stimulus onset. In an effort to uncover latent temporal relationships between frequency bands, we used principal component analyses (PCA) on each channel's spectrogram across trials, providing trial-wise components that we correlated with the corresponding trial RT. Across channels, stimulus-evoked spectrogram patterns explained significant variance in both encoding and test RTs, with increases in higher-frequencies followed by power decreases in lower frequencies. In addition, PCA on the spectrogram patterns revealed non-stimulus evoked theta and alpha activity components that exhibited opposite signs. That is, theta-alpha decoupling predicted RTs independent of stimulus onset. Finally, whereas spectrogram patterns across subregions of parietal cortex were equally predictive of semantic decision RTs, activity patterns in intraparietal sulcus (IPS) channels were significantly more predictive of retrieval RTs than spectrogram patterns in other parietal subregions. These data reveal that latent oscillatory states surrounding stimulus processing relate to goal-directed semantic decision-making and episodic memory encoding.

Disclosures: **A. Gonzalez:** None. **J.B. Hutchinson:** None. **M.R. Uncapher:** None. **J. Parvizi:** None. **A.D. Wagner:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: FNS Grant PP00A 106701

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FNS Grant 310030_143956

NIH Grant R01-NS16980

NIH Grant RR00169

Title: Differential structural maturation of neurons in distinct layers and subdivisions of the monkey entorhinal cortex during postnatal development

Authors: *O. PIGUET[1], L. J. CHAREYRON[2], P. BANTA LAVENEX[1], D. G. AMARAL[3], P. LAVENEX[1]
[1]Inst. of psychology, Univ. of Lausanne, Lausanne, Switzerland; [2]Dept. of Med., Univ. of Fribourg, Fribourg, Switzerland; [3]Univ. of California Davis, Sacramento, CA

Abstract: The entorhinal cortex is the main gateway for bi-directional communication between the neocortex and the hippocampal formation. Its superficial layers (II and III) represent the main entryways for much of the sensory information to be processed by the hippocampal formation, whereas its deep layers (V and VI) provide the main exitways through which processed information is sent back to the neocortex. Here, we performed stereological analyses to provide quantitative information on the postnatal structural development of neurons in the different layers of the seven subdivisions of the monkey entorhinal cortex. We found no differences in neuron numbers in any subdivision of the entorhinal cortex between newborn and adult monkeys. In contrast, we found differences in neuronal soma volumes, which were specific to certain layers and subdivisions. In rostral areas (Eo, Er and Ei, which altogether correspond to the rat lateral entorhinal cortex), there were no age differences in the volume of layer III neurons, which project to CA1. In contrast, we found an increase between birth and adulthood in the volume of layer V neurons, which receive projections from CA1 and the subiculum. In area Ei only, we found an increase in the volume of layer II neurons, which project to the dentate gyrus. In caudal areas (Ec and Ecl, which altogether correspond to the rat medial entorhinal cortex), the volume of layer III neurons, which are recipient of efferent projections from the presubiculum, was larger at birth than in adulthood; while the volume of layer V neurons was smaller at birth than in adulthood. Our quantitative stereological findings suggest: (1) an overall early maturation of the superficial layers of the entorhinal cortex, the main input pathways to the hippocampus; (2) an early maturation of the projections from the presubiculum to the caudal entorhinal cortex; and (3) a relatively later maturation of the projections originating in CA1 and the subiculum. Together with our previous findings in other structures comprising the hippocampal formation, our current results in the entorhinal cortex support the view that different hippocampal circuits exhibit distinct developmental profiles, which may subserve the emergence of specific “hippocampus-dependent” memory processes.

Disclosures: O. Piguet: None. **L.J. Chareyron:** None. **P. Banta Lavenex:** None. **D.G. Amaral:** None. **P. Lavenex:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.22/RR30

Topic: H.01. Animal Cognition and Behavior

Support: USD SURE grant

Funding from USD College of Arts & Sciences

Title: Role of the medial entorhinal cortex in temporal aspects of memory processing in rats

Authors: *T. A. FISHER, A. E. MORSE, A. C. CAMACHO, J. B. HALES
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Abstract: The formation and retrieval of episodic memories, which contain both spatial and temporal components, is dependent on the medial temporal lobes. The contribution of the hippocampus and adjacent medial entorhinal cortex (MEC) to spatial processing, with place cells and grid cells, respectively, and to spatial memory has been well established (O'Keefe and Dostrovsky, 1971; Hafting et al., 2005; Steffenach, et al. 2005; Hales et al. 2014). The hippocampus is also involved in temporal processing, containing "time cells" (MacDonald, 2011), and is important for temporal aspects of memory (Fortin, 2002). Despite the attention paid to the role of the MEC in spatial processing and memory, researchers have only begun to examine the temporal functions of the MEC. Recent studies have suggested that the MEC may play a role in hippocampus-dependent temporal processing as MEC lesions disrupt theta phase precession in the hippocampus, suggesting involvement of the MEC in temporal organization of hippocampal firing patterns (Schlesinger et al., 2015). However, the precise role of the MEC in temporal aspects of memory is still unclear. In order to directly examine the involvement of the MEC in temporal aspects of memory, we developed a temporal object sequence learning task. Rats with complete bilateral excitotoxic lesions of the MEC or sham lesions are presented with a sequence of five objects. After a brief delay, rats are given a sequential order probe to test memory for which of two objects was presented earlier in the sequence followed by an item memory probe (to test simple recognition memory). Results from both memory tasks will be discussed in terms of MEC involvement in temporal aspects of memory processing.

Disclosures: T.A. Fisher: None. **A.E. Morse:** None. **A.C. Camacho:** None. **J.B. Hales:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: UT Austin Institute for Neuroscience Training Grant

National Science Foundation CAREER Award #1453756

Title: Fast gamma rhythms predominate over slow gamma rhythms in superficial layers of medial entorhinal cortex

Authors: *J. B. TRIMPER[1], S. G. TRETTEL[2], E. HWAUN[2], L. L. COLGIN[3]
[1]Neuroscience, Ctr. for Learning & Memory, The Univ. of Texas At Austin, Austin, TX; [2]Univ. of Texas at Austin, Austin, TX; [3]Ctr. for Learning and Memory, Univ. of Texas At Austin, Austin, TX

Abstract: Slow gamma (~25-55 Hz) and fast gamma (~65-100 Hz) are distinct rhythms that are prevalent in the rodent hippocampus. However, the prominence of these rhythms in the superficial layers (II/III) of the medial entorhinal cortex (sMEC), a primary input to the hippocampus, has yet to be fully understood. In particular, although fast gamma is known to be present in sMEC at times when fast gamma occurs in the hippocampus, it remains unclear whether slow gamma occurs in sMEC at other times. One issue is that the detection of slow gamma episodes in the local field potential has been hampered by harmonics associated with nonlinearity in the sMEC theta waveform. Here, we recorded local field potentials and action potentials from sMEC in five freely behaving rats and developed a novel analytical approach to slow gamma event detection to address the extent to which slow gamma rhythms occur in sMEC. The occurrence of slow gamma activity was analyzed across different behavioral states and compared to the occurrence of fast gamma activity. Analyses revealed that slow gamma occurred significantly less often than fast gamma in sMEC. Although slow gamma rhythms occur prominently in the hippocampus during non-REM sleep, slow gamma rhythms in sMEC were as absent during non-REM sleep as during REM sleep and active wakefulness. In contrast, fast gamma rhythms occurred prominently, particularly during theta-related behaviors (i.e., ambulation and REM sleep). In summary, slow gamma was rarely detected in MEC superficial layers, whereas fast gamma was prevalent in MEC superficial layers during theta-related states. These results raise the possibility that fast gamma facilitates transmission of processed sensory information from MEC to hippocampus during active exploration. Additional studies are needed to explore the potential functional significance of fast gamma rhythms in MEC superficial layers during REM sleep.

Disclosures: J.B. Trimper: None. **S.G. Trettel:** None. **E. Hwaun:** None. **L.L. Colgin:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.24/RR32

Topic: H.01. Animal Cognition and Behavior

Support: Grants-in-Aid for Scientific Research on Innovative Areas #26119502

Title: Intrinsic projection of entorhinal layer Vb neurons of the rat

Authors: *M. ONODERA[1], S. OHARA[1], T. IIJIMA[1], M. P. WITTER[2], K.-I. TSUTSUI[1]
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Abstract: Layer V of the entorhinal cortex (EC), which receives inputs from the hippocampus and projects to telencephalic regions, is considered to play an important role in the hippocampus-memory system. Recently, layer V of the mouse medial entorhinal cortex (MEC), which is involved in spatial navigation, was found to be further divided into two sublayers: a deeper-sublayer which is immunopositive to transcription factor Ctip2 (LVb) and an upper-sublayer which is immunonegative to Ctip2 (LVa). The two sublayers also show distinct connectivity. Afferents from the hippocampus terminate in LVb but not in LVa, while the efferent projections to telencephalic domains originate from LVa, but not from LVb [Gulsen Surmeli et al., 2015]. The major projection targets of LVb neurons are still unclear. In addition, it has not been investigated whether this differentiation between LVa and LVb exist in the lateral entorhinal cortex (LEC), which likely processes information from different sensory modalities. In this study, we focused on both LEC and MEC of the rat and examined the unidentified projection targets of LVb neurons. We first examined the immunolabeling pattern of Ctip2 and PCP4 in EC, and confirmed that layer V of LEC can be divided into Ctip2/PCP4-positive LVb and Ctip2/PCP4-negative LVa, which is similar to MEC. We then examined the output of the LVb neurons by injecting a retrograde tracer into some telencephalic regions, such as the nucleus accumbens (NAc), retrosplenial cortex (RSC), and EC. LVb neurons were only labeled when the tracer was injected into EC, indicating that the major targets of LVb neurons are neurons within EC. To further examine this intrinsic projection in detail, we specifically labeled LVb neurons and examined the distribution of labeled fibers within EC. We found that LVb neurons innervate adjacent LVa and also the superficial layers (LII/III). To examine whether the LVb neurons make synapses with the telencephalic-projecting LVa neurons and the hippocampus-projecting LII/III neurons, we next conducted transsynaptic retrograde tracing experiments with rabies virus. After viral injection into either the telencephalic regions (NAc, RSC) or the hippocampus, LVb neurons in both LEC and MEC were transsynaptically labeled, suggesting that LVb neurons project to LVa and LII/III neurons. These anatomical data provide new insights that the LVb neurons mediate two circuits in the hippocampus-memory system: a hippocampal output circuit to telencephalic areas by projecting to LVa, and a feedback loop by sending information back to the EC-hippocampal loop via neurons in LII/III.

Disclosures: **M. Onodera:** None. **S. Ohara:** None. **T. Iijima:** None. **M.P. Witter:** None. **K. Tsutsui:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NRF-2015M3 C7A1031969

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SRC-2014051826

BK21+ program

Title: Object and visual contextual information processing in the perirhinal cortex and postrhinal cortex

Authors: *J. AHN, I. LEE
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Abstract: Prior research implicates that the perirhinal (PER) and postrhinal cortex (POR) are differentially engaged in object and visual contextual information processing, respectively. The evidence, however, has been obtained mostly from behavioral studies, and physiological evidence have been limited. In the present study, we measured multi-unit activities from both PER and POR simultaneously while rats performed an object and visual contextual memory task. The task took place on a linear track (46 x 7.5 cm) with a start box attached at the end of the track. A custom-made response box (13 x 6 x 13 mm) was positioned at the other end of the track, and was surrounded by an array of three LCD monitors. A pair of 3-dimensional objects (Phone and Owl) and contextual scene images (Zebra pattern and Pebble pattern) were used as stimuli, and appeared in an intermixed fashion within a session. In object trials, one of the object stimuli was attached to a rectangular opening (50 x 55 mm, 28 mm in depth) recessed in the front panel of the response box. When the rat approached the box, two LEDs installed inside the opening were turned on to illuminate the object. Each stimulus was specifically associated with a distinct behavioral response. For example, if Phone appeared as a stimulus, the rat had to push the response box to obtain reward underneath the box, but if Owl appeared, the rat had to nose-poke into a hole (diameter = 4 mm) recessed on top of the response box. The procedures were the same for scene context trials, except that the LEDs were not turned on, and contextual stimuli were presented via the LCD monitors. Single units were recorded from the PER and POR, and only the neurons with a sufficient number of spikes (>= 0.5 Hz) were analyzed. A majority of recorded units in the POR (75%, n= 21/28) exhibited a higher discriminability of the contextual stimuli than objects. In the PER, by contrast, the proportion of object-selective neurons (54%, n=

33/61) was larger than those showing context-selective responses (36%, n= 22/61; p<.01, Chi-square test). Further data acquisition is ongoing to obtain more neurons from the POR. Our results expect to provide the physiological evidence that the two rhinal corticle regions make distinctive contributions to object and visual contextual recognition memory.

Disclosures: J. Ahn: None. **I. Lee:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 MH60013

NIH R01 MH61492

ONR MURI N00014-16-1-2832

Title: Cholinergic modulation of interneurons in the medial entorhinal cortex

Authors: *K. A. YOUNG[1], M. C. BROWN[1], C. `. KELLEY[1], M. E. HASSELMO[2]
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Abstract: Medial septal projections (including cholinergic projections) to the medial entorhinal cortex (mEC) are thought to play a role in theta rhythmicity and the modulation of neuronal firing rate by running speed (Hinman et al., 2016; Neuron 91:666). There is mounting evidence in multiple cortical areas to suggest that acetylcholine communicates changes in behavioral state to the excitatory network via a disinhibitory interneuron circuit, such as the increase in sensory gain observed in visual cortex during locomotion (Fu et al., 2014, Cell 156: 1139). It has been shown in hippocampus that cholinergic release from the medial septum acts at muscarinic receptors in two interneuron cell types, with VIP+ interneurons showing direct depolarization and PV+ interneurons showing mixed responses including depolarization, hyperpolarization, and biphasic responses (Bell et al., 2015, J. Physiol. 593: 197). Thus, the effects of medial septal inputs to mEC may be mediated in part by direct cholinergic modulation of interneurons. We characterized changes in the intrinsic properties of SST+ and PV+ interneurons in mEC in response to carbachol, a cholinergic agonist, using whole-cell recordings in acute slice preparations. We found that SST interneurons depolarize during bath application of carbachol, while PV interneurons show biphasic or depolarizing changes in resting membrane potential. Cholinergic activation reduces the spike height, and shifts the frequency/current curve leftward in SST interneurons. While excitatory cells (stellate cells) in the mEC have been shown to demonstrate a strong resonant peak frequency in response to oscillatory current input that shifts

with cholinergic modulation (Heys et al., 2010, J. Neurophysiol. 104: 258), we observed neither strong resonance nor a peak shift in SST or PV interneurons. If interneurons in the entorhinal cortex participate in a similar canonical disinhibitory circuit as other areas of cortex, this cholinergic modulatory circuit could be used to indirectly affect the activity of excitatory cells in response to changes in behavioral state.

Disclosures: K.A. Young: None. **M.C. Brown:** None. **C.`. Kelley:** None. **M.E. Hasselmo:** None.

Poster

083. Hippocampal Circuits and Oscillations in Learning and Memory

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 083.27/RR35

Topic: H.01. Animal Cognition and Behavior

Title: Differential effects of diazepam on exploration are modulated differently by ventral and dorsal hippocampal theta activity

Authors: *Y. ZHAN[1], B. SI[2], Y. HAN[1], A. L. VYSSOTSKI[3]
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Abstract: Free exploration in the novel environment depends on the locomotor activity and the willingness to approach unknown territory. Although hippocampus and the circuit between the hippocampus and the prefrontal cortex underlies the exploration and the anxiety-induced behaviors, how neural activity in these structures modulates the exploratory intention and the locomotion is poorly understood. Previous studies have shown that treatment of anxiolytic compound diazepam exerts pronounced effects on theta activity in the brain. Using dimensionality emergence assay consisting of a large open filed and a home shelter in the presence of diazepam, we measured two dimensions of exploratory behaviors characterized by moving motions and expanded novelty as well as the theta activities in the ventral hippocampus (vHPC), dorsal hippocampus (dHPC) and prefrontal cortex (PFC). When separating the exploration behavior into slow and fast motions, we found that diazepam increased progression path while decreased the lingering path. Diazepam produced opposite effects on the theta frequency in the vHPC and dHPC. Together with the effects of diazepam in the new areas that the animals never explored, diazepam increased vHPC theta frequency in the new area but not in the familiar areas. Theta coherence between the dHPC and the mPFC signals the transitions between the vicinity of home and the area far away. Our findings demonstrates that diazepam further disinhibits fast long-distance travel and lowers level of rumination around its local body

position. The effects of diazepam in the vHPC in the new area only highlight the roles of this brain region in exploring unknown territory. The change of frequency-speed fitting relationship illustrates that the drug could modulate locomotion through theta frequency. Finally theta synchronization between dHPC and PFC underlies novelty seeking and leaving during exploration.

Disclosures: **Y. Zhan:** None. **B. Si:** None. **Y. Han:** None. **A.L. Vyssotski:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 084.01/RR36

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Global remapping in the hippocampus and entorhinal cortex during spatial navigation and its relationship to choice accuracy in a novel two-platform water task in rats

Authors: ***J. Q. LEE**[1], R. J. MCDONALD[2], R. J. SUTHERLAND[3]
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Abstract: The hippocampus (HPC) and entorhinal cortex (EC) encode both cue and place information. Previous reports on cue and place representation in HPC and EC have examined single neuron and population activity during passive exploration of an environment or during memory task performance guided by places or cues. To better understand representations of cues and places in HPC and EC, and how these types of information interact during goal-directed navigation, we investigated population activity during memory retrieval in HPC subregions (dentate gyrus, CA3, and CA1) and EC along the entire dorsoventral and mediolateral axis in a novel water task with two visibly distinct platforms. We used immediate early genes Arc and Homer1a to measure neural activity. Our results demonstrate that, after training, relocation of platforms to previously empty locations in the pool induces global remapping of the population code that is associated with altered navigation and rapid learning of new cue-place information. By contrast, after training, exchanging platform locations induces much less change in the population code and is associated with more persistent navigation to previous goal locations. These findings highlight the importance of population recoding to memory-guided choice accuracy, and further characterize cue and place memory representation in the hippocampus, and how these types of memory interact to control behavior.

Disclosures: **J.Q. Lee:** None. **R.J. McDonald:** None. **R.J. Sutherland:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI Grant Number 16K14561

JSPS KAKENHI Grant Number 16H01290

Title: Spatial representations of the other and self in the hippocampus

Authors: *T. DANJO, S. FUJISAWA
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Abstract: Spatial navigation is based on the function of the hippocampus, especially of its 'place cells', which are activated in association with spatial positions of the animal. Spatial navigation has been conceptualized into two forms. The first one is the path integration or egocentric navigation, in which the current position is recognized by integrating the information of the previous position and other sensory inputs such as velocity, time duration and direction. The second is the map-based allocentric navigation, in which animals understand their positions and destinations by referring 'the cognitive map' in the hippocampus, which represents absolute place of the environment. Neuronal and network mechanisms of the path integration have been progressively elucidated, however, those of the allocentric navigation and the cognitive map have largely remained unknown.
In this study, we aimed to describe, by regarding the position of the other animal as an example of allocentric place, how it is represented in the hippocampus, while the other animal is moving around the environment. For this purpose, we designed a set of behavioral T-maze tasks, performed by a pair of rats, in which one animal is required to observe the other animal and decide its behavior according to the other animal's location. By recording single unit activities from the observer's hippocampus (CA1), we ask whether and how the other animal's position is encoded during this observational task. We show that the other's spatial information is jointly encoded in the self's place cells. Several other findings, such as theta phase precession as a function of the other's place, dissociative representations of the other's place and self's future direction, the mirror feature, the reconstruction of the other's positions will also be presented in this poster.

Disclosures: T. Danjo: None. **S. Fujisawa:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI Grant Number JP26350992

Title: Spatial representation and firing periodicity of hippocampal CA1 pyramidal neurons in the freely behaving monkey

Authors: *Y. HAZAMA, R. TAMURA
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Abstract: Several studies on hippocampal neurons in the monkey have reported that an increase in their firing activities depending on the animal's location. In most of these studies, however, monkeys seated in a chair while performing spatial tasks using virtual reality systems or vehicles so that the effect of self-locomotion on the spatial representation of place cells is unclear. Also, the existence of robust slow rhythmic modulation (theta modulation) of spike pattern that is known to appear in the hippocampus of rodents has not yet been examined in freely behaving primates. To address this issue, here we recorded hippocampal neural activities in the monkey performing a shuttle-movement task under a freely behaving condition.
We trained a macaque monkey to shuttle on a linear track (3.8 × 0.9 m) for food rewards delivered from pellet dispensers set at both ends of the track. After the monkey learned this task, a position-adjustable tetrode was chronically implanted in the hippocampus. In the recording session, the electrode was gradually advanced toward the CA1 pyramidal cell layer; CA1 neuronal activities were recorded while the monkey performed the shuttle-movement. Recorded spikes were sorted based on their waveform characteristics; a clustering software isolated single units; firing rate maps and power spectrum of spike-train autocorrelogram were computed for each single unit.
Of 83 putative pyramidal neurons sampled in the CA1, a place field was observed in 17 neurons (place cells, exhibiting spatial information value above the chance level). The proportion of place field area (the area in which a neuron fired above 20% of peak firing rate) in the entire area visited by the monkey of the linear track was 34.4% on average. The degree of theta modulation calculated by the power spectrum showed low 'theta index' (3.8 on average), and only 2 neurons out of 17 exhibited significant theta modulation. The monkey's locomotion speed had significant positive correlation with firing rate of place cells and the negative relationship with their place field size.
The presence of place cells in the monkey hippocampus provides compelling evidence that the primates also have a similar cognitive map mechanism to that of other mammals; the absence of

the rhythmic slow activity, which is recognized as the encoding carrier of spatial information in rodent hippocampus, indicates that the primate hippocampus has a different information encoding protocol than rodents.

Disclosures: Y. Hazama: None. **R. Tamura:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 084.04/SS3

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Bilateral lesions of the lateral mammillary nucleus impair spatial learning in rats

Authors: *D. M. SKINNER, S. C. WAYE, R. L. BUNGAY, G. M. MARTIN
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Abstract: To navigate successfully an animal must have knowledge of location and directional heading. These two components of navigation are well represented in a spatial network in the mammalian brain that contains place cells, grid cells, and head direction (HD) cells. It has been suggested that the HD signal originates sub-cortically in the reciprocal connections between the dorsal tegmental nucleus (DTN) and the lateral mammillary nucleus (LMN). Lesions to the LMN or DTN have been shown to disrupt HD cell firing in downstream structures such as the anterior dorsal nucleus of the thalamus and the postsubiculum. Lesions to the DTN have also been shown to produce severe impairments in directional heading on a foraging task and in directional learning in a water maze. In the present study rats with bilateral electrolytic lesions of the LMN were compared to sham controls on spatial tasks thought to be solved using directional heading. Rats were first trained on either a direction problem or a rotation problem in a water T-maze. LMN-lesioned rats were impaired relative to sham controls, on both the first block of eight trials and on the total number of trials taken to reach criterion. In the food-foraging task, rats were trained to leave a home cage at the periphery of a circular table, find food in a food cup at the center of the table, and return to the home cage. Again, LMN-lesioned rats were impaired relative to sham rats, making more errors on the return component of the foraging trip. These results build on previous behavioural and cell-recording research examining the HD cell system and demonstrate the importance of the direction system to spatial learning.

Disclosures: D.M. Skinner: None. **S.C. Waye:** None. **R.L. Bungay:** None. **G.M. Martin:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: KAVLI Foundation, NWB-4-HPC

NIH Grant 1R01MH105174-01

Title: An advanced data software architecture for neurodata without borders (NWB) to enable efficient management, use and sharing of neurophysiology data

Authors: *O. RUEBEL[1], A. TRITT[1], D. CAMP[1], E. F. CHANG[3], D. DONOFRIO[1], L. M. FRANK[4], F. T. SOMMER[5], K. BOUCHARD[2]
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Abstract: To maximize the return on investment into creation of neuroscience data sets and enhance reproducibility, it is critical to share data through standardized and extensible data model and management solutions. In addition to standardizing data and metadata, support for fast data read/write and high-performance, parallel data analysis are critical to enable labs to keep up with ever growing data volumes. The Neurodata Without Borders: Neurophysiology (NWB-N) effort was an important step towards generating a unified data format for cellular-based neurophysiology data for a multitude of use cases. To enable broad adoption of NWB-N, easily accessible tools and an advanced software strategy aimed at facilitating the use, extension, integration, and maintenance of NWB-N are critically needed. The Kavli sponsored NWB-4-HPC project aims to ensure that the software instantiation of NWB-N adheres to these principles and enables efficient management and processing of large-scale neuroscience data sets. Here, we apply software engineering principles to create an advanced software architecture and define abstractions to enable separation of the NWB specification language, format specification, data storage, and data API(s). The NWB-spec API makes format specifications easily accessible to end users and enables the effective design of format extensions customizable to lab needs. PyNWB, a Python library for NWB, then defines a high-level API for interacting with NWB data to facilitate efficient data read/write and integration of the format with user datasets and code bases. An integrated data-build API then manages the integration of PyNWB UI objects with the NWB format specification to create abstract representations of NWB data containers. Finally, containers are translated to and from NWB-N files on disk via a read/write layer that has been abstracted to enable multiple storage options. This strategy allows us to effectively decouple the various aspects of the system and create stable and easy-to-use APIs for users and

developers that provide critical abstractions from NWB internals. We demonstrate the application of our system to diverse electrophysiology use cases provided by the Frank Lab (USCF), Chang Lab (UCSF), and Bouchard Lab (LBNL) among others. Our architecture empowers users to easily access, use, and analyze NWB data, integrate NWB with user code bases, and develop new extensions for NWB-N. This novel software architecture lays the foundation for the design of advanced APIs for data management, query and discovery, and integration of NWB-N with state-of-the-art data analytics codes optimized for high-performance computing systems.

Disclosures: O. Ruebel: None. **A. Tritt:** None. **D. Camp:** None. **E.F. Chang:** None. **D. Donofrio:** None. **L.M. Frank:** None. **F.T. Sommer:** None. **K. Bouchard:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: NINDS Grant U01NS090537

NIMH Grant F30MH109292

Howard Hughes Medical Institute

Flatiron Institute

Title: Modular polymer probe-based system enables long-lasting, high-quality recordings from distributed circuits in freely behaving animals

Authors: *J. E. CHUNG[1], J. L. FAN[2], H. R. JOO[1], D. F. LIU[3], C. R. GEAGHAN-BREINER[2], S. CHEN[4], J. PEBBLES[4], A. TOOKER[4], K. Y. LEE[4], J. F. MAGLAND[5], A. H. BARNETT[5,6], L. F. GREENGARD[5], V. TOLOSA[4], L. M. FRANK[7,8,9]
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Abstract: Brain functions depend on millisecond timescale interactions across networks which span numerous structures, and there is a need for technologies that enable the observation of these interactions and their evolution across the lifespan. A suitable technology will provide 1)

modularity to target multiple regions in a distributed circuit, 2) resolution to reliably isolate single neurons, and 3) longevity of single unit recording for months. We have therefore developed a penetrating polymer recording array system with a modular, stacking headstage that supports up to 1024 channels of recording. Each of the sixteen independently targetable modules consists of a 4-shank 64-channel polymer array, wire-bonded to a printed circuit board (PCB) with an amplifying, digitizing, and multiplexing chip. When 16 modules are fully-assembled, the system takes up a volume of 22 mm x 22 mm x 25 mm. As an initial demonstration, we implanted the full 1024 channel system into a rat. Each polymer array was implanted utilizing an approach where arrays are bound to removable silicon stiffeners using polyethylene glycol, a water-soluble adhesive, for insertion into the brain (Tooker et. al. 2013). From the 8 modules that yielded single units, we recorded over 375 well isolated units across pre-limbic cortex, anterior cingulate cortex, orbitofrontal cortex, and nucleus accumbens shell. We also acquired bilateral local field potentials from the CA1, CA3, and dentate gyrus areas of the hippocampus. Separately we quantified the longevity of the devices and found that flexible multielectrode polymer probes can yield high quality single units for over 10 months from implantation (time of experiment termination). This modular system enables chronic recording from hundreds of neurons across distributed circuits in awake, freely behaving animals.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

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Support: NIMH NRSA F31MH111214

Simons Collaboration for the Global Brain Grant A123993

NIH R01 MH090188

HHMI

Title: Reactivation of nucleus accumbens neurons during awake dorsal and ventral hippocampal sharp-wave ripples

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UCSF Med. Scientist Training Program, Kavli Inst. for Fundamental Neurosci., [3]Howard Hughes Med. Institute, Kavli Inst. for Fundamental Neurosci., Dept. of Physiol., Univ. of California, San Francisco, San Francisco, CA

Abstract: Learning of a complex spatial task requires that the actions taken to acquire reward become closely linked with the spatial characteristics of the environment. This association process is supported in part by interactions between the hippocampus (HPC) and nucleus accumbens (NAc). Hippocampal network events known as sharp-wave ripples (SWRs) are well suited to contribute to this process, as SWRs reactivate hippocampal ensembles in a manner that can recapitulate prior experience. In particular, awake SWRs occur during periods of immobility that punctuate ongoing behavior and may be important for consolidating associations between recently navigated spatial paths and their reward outcomes. NAc cells associated with reward sites have been shown to reactivate with SWRs during sleep, but whether NAc cells reactivate during awake SWRs and whether these cells encode other important aspects of the learned experience remains unclear. Furthermore, prior studies focused on the dorsal hippocampus (dHPC), while the ventral hippocampus (vHPC) has a substantially larger direct anatomical projection to the NAc. To understand how awake interactions between the dHPC, vHPC, and NAc support spatially guided reward learning, we recorded extracellular activity from all three regions simultaneously in rats learning a spatial working memory task with changing reward contingencies. We found a subset of NAc neurons that showed both an association with various task elements as well as significant changes in activity during either dHPC SWRs, vHPC SWRs, or both. We also observed evidence for structure in this reactivation, as specific pairs of NAc cells were coactivated during individual SWRs in relation to how they fired together during behavior. Our findings suggest that NAc neurons representing particular types of task-relevant information encoded in the NAc are engaged during awake SWRs. Moreover, SWR-related activity in the NAc may reflect distinct types of spatial and task associations reflective of dHPC and vHPC input.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: Howard Hughes Medical Institute

5F30MH097356-02

R01MH090188

Title: Continuous rhythmic alternation between divergent spatial codes in the hippocampus

Authors: *K. KAY[1,2], J. E. CHUNG[1,3], M. SOSA[1,3], J. S. SCHOR[1,3], M. P. KARLSSON[1], M. C. LARKIN[1], L. M. FRANK[1,4,2]
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Abstract: How is it possible to think about the future? Imagination and planning are essential to cognition and associated with particular brain regions, yet remain poorly understood. Prior psychological and ethological work implicates a neural mechanism for future-thinking that (1) sustains a stable representation of the future over time ("hold in mind"), (2) selects between different future representations, and (3) operates rapidly during active behaviors, when sensory/motor inputs are in flux. However, no known candidate neural mechanism supports these three essential capacities concurrently.
Two major clues at the neurophysiological level have been found in the hippocampus, a brain structure that represents spatial location and, critically, is required for psychologically and behaviorally instantiated future-thinking. The first clue is hippocampal replay (reviewed in Buzsaki 2015), a pattern of neural firing that occurs in brief bouts (~100 ms) when subjects are at rest. The second clue is hippocampal theta sequences (reviewed in Redish 2016), a pattern of neural firing that occurs periodically at ~8 Hz (125 ms) when subjects move through space. Both replay and theta sequences are now known to represent upcoming spatial experience, consistent with roles in planning. However, the properties of replay and theta sequences, while complementary, respectively indicate neural mechanisms that have restricted roles in planning: on one hand, since replay occurs at rest it cannot rapidly respond to changing sensory/motor input (capacity 3), while on the other hand it is unknown how theta sequences enable sustained representation of multiple future scenarios (capacities 1 and 2).
To investigate this matter, we recorded neural activity in the hippocampus of rats navigating a spatial memory maze. We found neurons in CA1, CA2, and CA3 representing two spatially opposed future locations routinely firing in alternation, doing so continuously and at a rapid characteristic frequency (8 Hz). This continuous rhythmic alternation was strongest when an upcoming behavioral choice requiring spatial memory was imminent, and moreover was most prevalent in upstream hippocampal subregions (CA2/3). Additional results further indicated that alternation was common and engaged hippocampal neural populations. These findings extend past work on theta-associated representational switching (Jezek et. al. 2011) and "skip" firing (Deshmukh et. al. 2010, Brandon et. al. 2013) to an adaptive function, and identify a temporally- and anatomically- specific neural mechanism capable of supporting stable, selective, and fast planning in the hippocampus and beyond.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: NIH RO1MH105174

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Jane Coffin Childs Memorial Fund Postdoctoral Fellowship

Title: Unique and general representations of experience are linked in hippocampal-cortical networks

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Abstract: In memory, unique episodes of experiences are linked to more general semantic knowledge. In the context of spatial memory, representations of specific paths might be linked with the general concept of a path. The hippocampus is critical for the formation and retrieval of memories for individual events, while cortical networks are implicated in the representation of generalized knowledge. It remains unclear how associations between individual and general representations of experience are expressed in hippocampal-cortical networks. We therefore examined hippocampal and prefrontal cortical activity in rats navigating in an environment with multiple distinct trajectories. While hippocampal place cell activity was restricted to individual locations and trajectories, we found prefrontal cells display diverse activity patterns. A subset of prefrontal cells showed high similarity in activity across different trajectories, a property consistent with a generalized task related representation for these locations. Strikingly, hippocampal sharp-wave ripple reactivation of trajectory related location representations preferentially engaged prefrontal cells that generalized across locations. As a result, coordinated reactivation of prefrontal cortical activity was similar for distinct reactivated hippocampal place representations. Our findings suggest hippocampal representations specific for individual experiences are mapped onto cortical representations for features shared between multiple individual experiences. The general and specific mapping is maintained during both ongoing experience and memory processes. We suggest this enables the formation of associations between individual experiences and their shared features.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Support: NSF GRFP Grant No. 1144247

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Title: Apolipoprotein E4-induced hippocampal network activity deficits reflect cell-type-specific gains of toxic function

Authors: *E. A. JONES[1,2], A. K. GILLESPIE[3], Y.-H. LIN[4], S. YOON[1], L. M. FRANK[5,3,4], Y. HUANG[1,6,2,7]
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Abstract: Apolipoprotein (apo) E4 is the major genetic risk factor for Alzheimer's disease. However, controversy remains as to whether apoE4-induced deficits result from a loss of function or a gain of toxic function compared to apoE3. Previously, we reported that aged female mice with the human apoE4 gene knocked in at the mouse apoE locus (apoE4-KI) show two functional phenotypes in hippocampal sharp-wave ripples (SWRs), a network activity signature that has been linked to memory processes. These phenotypes include reduced SWR abundance and reduced slow gamma power coincident with SWRs. Following this finding, we examined which aspects of these phenotypes were loss or gain of function by deleting apoE from all neurons (apoE4-fKI/Syn-Cre) or all cells (apoE-KO), and comparing these mice to WT, apoE3-KI, apoE4-KI, and apoE4-fKI/Dlx-Cre mice, which have apoE4 deleted in inhibitory interneurons. We found that apoE4-induced reduction in SWR abundance reflects a gain of toxic function, as deletion of apoE does not cause this phenotype. This deficit is likely driven by excitatory neuron populations, as pan-neuronal deletion but not interneuron-specific deletion prevented the reduction in SWR abundance. Similarly, apoE4-induced reduction in coincident slow gamma power throughout the hippocampal circuit reflects a toxic gain of function, as deletion of apoE does not cause this phenotype. However, this deficit is specific to apoE4 in inhibitory neurons, as both apoE4-fKI/Dlx-Cre and apoE4-fKI/Syn-Cre mice showed no deficit. These data suggest that apoE4-induced attenuation of SWR abundance and SWR-associated slow gamma power reflects a toxic gain of function and could potentially be mitigated by reducing neuronal apoE.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: NINDS grant U01NS090537

NIMH grant F30MH109292

Title: MountainSort: A fully automated approach to spike sorting

Authors: ***J. MAGLAND**[1], J. E. CHUNG[2], A. BARNETT[3], V. M. TOLOSA[4], A. C. TOOKER[4], K. Y. LEE[4], K. G. SHAH[4], S. H. FELIX[4], L. M. FRANK[5], L. F. GREENGARD[1]
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Abstract: Extracting spike times and neuron labels from raw, multi-channel, continuously sampled data is referred to as spike sorting. Currently, such analyses lack standardization and typically rely on manual input, making it difficult to maintain data provenance and assess the quality of the data underlying scientific results. Furthermore, current approaches require large amounts of both computer and human time. Here we describe an automated clustering approach, cluster quality metrics, and an associated software package that addresses these problems. We show that our approach has accuracy comparable to or exceeding that achieved using standard manual or semi-manual techniques and runtimes much faster than acquisition time. Moreover, a single choice of parameters in the algorithm is effective for a variety of electrode geometries and across multiple brain regions. We validate our algorithm and compare it with other publicly available spike sorting methods using (a) a tetrode recording in the CA1 region of rat hippocampus, (b) a 16 channel polymer probe recording in the rat prefrontal cortex, (c) a publicly available dataset with known ground truth as measured by a juxtacellular probe, and (d) simulations using background signal extracted from real recordings. This software has the potential to enable reproducible and automated spike sorting of much larger scale recordings than is currently possible.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: Research Council of Norway

Kavli Foundation

Title: How is a place field generated? Developing a method for the functional identification of inputs to a single hippocampal neuron

Authors: *R. JACOBSEN, F. DONATO, R. R. NAIR, C. KENTROS, M.-B. MOSER, E. I. MOSER
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Abstract: The hippocampus receives inputs from a variety of spatially modulated cells in the medial entorhinal cortex, including grid, border and head direction cells. These inputs are thought to be integrated by individual hippocampal cells and influence the properties of their place fields, which represent an animal's specific location in space. In particular, it has been hypothesised that these spatially localised firing patterns can be achieved by integrating inputs from grid cells of different modules. However, which entorhinal cortical cell type(s) and grid cell modules are involved in the formation of a single cell's place field remains unclear.
We are developing a method that utilises a developmental approach to achieve extreme virus dilutions. This enables us to target a single cell in the CA3-subfield of the hippocampus with a pseudotyped and G-protein deleted rabies virus expressing Channelrhodopsin-2 (ChR2). The retrograde, monosynaptic transfer of the virus from this single cell will allow us to detect its inputs in layer 2 of the medial entorhinal cortex. Using electrophysiology and light-mediated activation of ChR2 we can thus identify the spatial properties of these input cells while the animal is exploring an open field environment.
By targeting a large group of hippocampal cells with this method, we have been able to identify cells in the medial entorhinal cortex that provide direct, monosynaptic input to the hippocampus, including grid and aperiodic spatial cells. With further refinement of this method, we aim to target, and functionally identify the inputs to, a single cell in CA3. Achieving this will not only

allow us to define the inputs involved in the generation of place fields, but also further our understanding of neuronal integration at the level of single cells.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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the Kavli Foundation

Title: Impaired grid coding in old mice

Authors: *Q. CAO[1,2], C. MIAO[2], E. I. MOSER[2], M.-B. MOSER[2]
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Abstract: Ageing is often correlated with declining cognitive functions, including spatial orientation and memory. Loss of spatial orientation and memory abilities might reflect dysfunctions in circuits of the hippocampus and entorhinal cortex. In transgenic mice expressing mutant human tau in entorhinal cortex, aged animals have impairments in grid cells as well as spatial memory (Fu et al., Neuron 2017). Here we asked whether grid cells exhibit age-related impairments also in normal animals. Tetrodes were implanted in the medial entorhinal cortex (MEC) of young mice (3 to 4 months old) and old mice (>28 month old). Cells were recorded during free running in a 1 m × 1m box. Grid cells were defined by the 99th percentile of a shuffled distribution of the data from the young mouse group. Fewer cells passed the grid-score criterion in old mice compared to young mice. The grid score of the few grid cells passing the criteria in old mice was significantly lower than in young mice. The impairment in grid scores was associated with reduced spatial stability of the grid pattern. These changes in the grid-cell population were not related to any detectable changes in behavior. Running speed and coverage of the box were not different between the old and the young mice. The findings point to impairments in the grid code a possible contributor to declines in spatial orientation and memory functions in normally aging animals.

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Poster

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Support: Norwegian Research Council Centre of Excellence Grant

Kavli foundation

Title: A brainstem/basal forebrain/cortical circuit for the neuronal coding of locomotion speed

Authors: ***N. TANKE**[1], M. M. CARVALHO[1], E. KROPFF CAUSA[2], M. P. WITTER[1], M.-B. MOSER[1], E. I. MOSER[1]
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Abstract: Speed cells in the medial entorhinal cortex (MEC) form a functionally distinct group of cells whose firing rate show either a positive or a negative linear correlation with locomotion speed. However, the origin of the speed signal in MEC is currently poorly understood. Previous studies have shown that stimulation of the pedunculopontine tegmental nucleus (PPN), a functional component of the brainstem's mesencephalic locomotor region (MLR), is known to induce locomotion. Moreover, speed cells have been reported in this area; but it remains unclear whether and how signals from these neurons reach MEC. In this study, we investigated the possible implication of PPN for speed coding in MEC. Simultaneous anterograde and retrograde tracer injections, respectively in PPN and MEC, showed an indirect connection between these two areas, with a strong overlap between labelled PPN axons and MEC-projecting cell bodies in the basal forebrain, specifically the ventral medial septum and diagonal band of Broca (MS/DB). Chronic *in vivo* tetrode recordings during free foraging in an open field confirmed the presence of speed cells, with either a positive or a negative linear speed-rate relationship along this putative PPN-MS/DB-MEC circuit. In all three brain areas, positive speed cells showed prospective firing properties, consistent with the hypothesis that this speed signal may derive from a motor efferent copy in the brainstem. Conversely, the firing rate of negative speed cells correlates more closely to past speed. Optogenetic stimulation of channelrhodopsin-2-expressing neurons in PPN was followed, at regular latencies, by activation of a wide range of cells in both MS/DB and MEC, including speed cells, implicating the PPN as an upstream modulator of speed cell firing in both MS/DB and MEC. Together, our results suggest the presence of a functional connection between PPN, MS/DB and MEC for speed coding in the brain, with a possible relevance for higher order spatial mapping and navigation.

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Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Title: Precise control of theta frequency by acceleration during spatial navigation

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Abstract: The theta rhythm organizes neural activity in the hippocampus and entorhinal cortex of rats, packing related information for the purpose of local network computations (Gupta et al., 2012; Mizuseki et al., 2009). An additional coding role for the theta cycle has been proposed, explaining the correlation between spiking position and theta phase found in spatial fields (O'Keefe and Recce 1993, Hafting, Fyhn et al. 2008) as a result of a strict linear dependence of theta frequency on running speed (Geisler, Robbe et al. 2007, Jeewajee, Barry et al. 2008). However, very little is known about the modulation of theta frequency by other navigational variables that might interfere with this proposed mechanism. By means of a recently introduced protocol that allows the disentanglement of kinematic variables, we here show that the theta band frequency of both local field potential oscillations and single cell rhythmic spiking is modulated by positive-only acceleration rather than speed. This non-linear relationship, confirmed in free foraging open-field experiments, makes the integral of theta frequency path-dependent (nonholonomic) and in consequence non-univocally related not only to displacement but also to any other kinematic variable. Our results suggest that variations in theta frequency rather reflect a precise mechanism for speeding up computations in the entorhinal-hippocampal circuits. This

global mechanism, triggered by highly specific behaviors, could produce a greater number of computational epochs per second, thus reducing systematic errors in linear calculations of trajectory.

Disclosures: E. Kropff Causa: None. **J.E. Carmichael:** None. **E.I. Moser:** None. **M. Moser:** None.

Poster

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Kavli Foundation

Title: Environmental influences on the grid pattern

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Abstract: Grid cells, found in the medial entorhinal cortex, produce a periodic hexagonal firing pattern covering the surroundings of a rat. Recent works have shown that the pattern is related to the geometry of the environment in a particular way. Specifically, the grid pattern in a square enclosure aligns to the box axis with a 7.5 degree offset and displays a shearing-induced elliptical distortion. The cause for this asymmetrical and particular relationship is unknown but it could stem from behavioral specifics from when the animal first encountered the environment or, alternatively, a particular relation between the boundaries or the geometry of the environment and the grid. Clarifying this issue may provide an explanation to how the grid anchors to the outside world.
To further investigate the relationship between the grid pattern and environment we used differently sized and shaped enclosures to tease out whether there exists any specific rules for how the grid orients or distorts in relation to environmental boundaries or shape. Moreover, we recorded grid activity in animals as they first encountered a new recording enclosure. The data was analyzed on a local scale using a sliding window 2d autocorrelation that provided local measures of orientation, spacing and elliptic distortions. The novelty data was also subjected to a

sliding window analysis, but using, for each cell, a crosscorrelation measure between the first and a later session. This method describes the change of the grid between different sessions. Grid patterns were observed in all environments, including half-circles, triangles and irregular shapes, but the periodicity of the pattern required a certain box size to be visible. Unlike the grid in a square enclosure, the grid displayed highly varying orientations and distortions in differently shaped environments., suggesting the entire environmental geometry influenced the layout of the grid. The analysis of the local shape of the grid showed that it would typically have specific orientations and distortions in relation to the corners of the environment. These particulars, however, could possibly be explained by the increase in grid scale seen in the middle of the environment (barrel distortion). Some grid modules that differed from these norms had ruptures in the hexagonal structure where pentagonal dislocations were found.
In conclusion, the grid pattern is maintained across a variety of regular and irregular shapes but displays complex distortions depending on shape, possibly related to both local and global geometrical features, as well as behavioral-related parameters such as novelty and exploration.

Disclosures: **M. Hagglund:** None. **M. Mørreaunet:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

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Title: Object-vector cells in the medial entorhinal cortex

Authors: ***Ø. A. HØYDAL**, E. R. SKYTØEN, M.-B. MOSER, E. I. MOSER
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Abstract: The medial entorhinal cortex (MEC) houses a diversity of cell types with distinct functions in the representation of space, including head-direction cells, border cells, speed cells

and grid cells. So far nearly all data for studies of these cells have been collected during foraging in open spaces. Little is known about whether cells in the MEC incorporate information about the location of discrete objects in the environment, which likely serve as references for navigation. Here we recorded from single MEC units while mice explored enclosures with salient three-dimensional objects. Approximately 15% of the neurons recorded in layers II-III had firing fields defined by the location of the object. These cells showed robust increases in activity whenever the mouse was at a certain direction and distance relative to the object, independently of the direction of movement through the location. When the object was displaced, the firing fields of these object-vector cells moved accordingly, so that tuning to object distance and direction remained constant. The tuning was unspecific to object identity; introducing objects of different sizes and shapes at different locations generated firing fields at a similar direction and distance relative to each object. Moreover, the vectorial representation was present from the first exposure to an object or to a novel environment. Object-vector cells retained their firing properties across environments, rotating coherently with the directional preferences of head direction cells and other object-vector cells, suggesting that object-vector cells are part of a universal and rigid representation. The majority of object-vector cells were distinct from other entorhinal cell types but cells with conjunctive response features were present. Taken together, these observations suggest that object locations are included in the metric representation of the MEC, with a distinct population of cells encoding the animal's position in relation to these objects.

Disclosures: **Ø.A. Høydal:** None. **E.R. Skytøen:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

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Title: Parvalbumin and somatostatin expressing interneurons contribute differentially to spatial coding in the medial entorhinal cortex

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Abstract: The medial entorhinal cortex (MEC) is a central part of the mammalian spatial representation system. A key component of this system is the grid cell, whose firing fields tile the available space in a remarkably periodic hexagonal pattern. Grid cells are unique in the sense that their firing pattern cannot be traced back to the animal's sensory inputs, pointing instead to intrinsic circuits of the spatial representation system as the source of the periodicity. Recent theoretical models have identified the inhibitory network of the MEC circuit as a potential critical element in the formation of grid patterns. Inhibitory networks of MEC consist of several classes of GABAergic interneurons but their relative contribution to grid formation remains elusive. In the present study, we employed a pharmacogenetic approach to silence specifically either parvalbumin (PV)- or somatostatin (SOM)-expressing interneurons while spatially modulated cells were recorded in the MEC of freely moving mice. Two different Cre lines of transgenic mice PV-Cre and SOM-Cre - were used. The mice were injected in MEC with Cre-dependent adeno associated virus (AAV) expressing the pharmacologically selective designer Gi-protein-coupled muscarinic receptor hM4D, which led to selective expression of hM4D receptors in PV and SOM interneurons, respectively. Subsequent systemic injection of Clozapine-N-oxide (CNO), a specific ligand of hM4D, caused selective inactivation of the respective interneuron subtypes. CNO antagonized the hexagonal activity structure of grid cells but only when the hM4D receptor was expressed in PV-positive interneurons. The impairment was expressed as increased firing between the grid fields and was accompanied by decreased speed modulation in simultaneously recorded speed cells. There was no change after CNO in the grid pattern of SOM-Cre mice; however, in these mice the silencing instead caused a specific decrease in the firing pattern of cells with aperiodic spatial firing fields. Firing rates of grid cells increased after CNO in both mouse lines. No changes could be seen in the spatial firing properties of border cells or the directional tuning of head direction cells. Taken together, these findings point to distinct roles for PV and SOM-expressing interneurons in the local dynamics enabling the expression of periodic and aperiodic firing patterns in spatially modulated cells of the MEC.

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Poster

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Title: Functional characterization of layer Va cells in the medial entorhinal cortex

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Abstract: The medial entorhinal cortex and neighboring pre- and para- subiculum are thought to represent space through a set of functionally specialized cell types: grid cells, border cells, head direction cells and speed cells. To date, much of the experimental and theoretical work has focused on the interactions between these cells and the place cells of the hippocampus, with little attention paid to the outputs from the entorhinal cortex to the rest of the brain. Recently, Surmeli et al (2016) discovered that the vast majority of the output from the entorhinal cortex to non-hippocampal targets originates from a thin strip of cells in superficial layer V, called layer Va. The cells in layer Va are further distinguishable from cells in neighboring layers because they have very large cell bodies, dendritic arbors that stay largely within the sublayer, and express the transcription factor ETV1. Another recent study found that these cells play a critical role in the induction of cFos in the medial prefrontal cortex and expression of fear behaviors following fear conditioning (Kitamura et al., 2017). However, nothing is known about the functional characteristics of these cells *in vivo*. To address this issue, we injected an adeno-associated virus (AAV) engineered for efficient retrograde transport and carrying cre-recombinase (Tervo et al., 2016) into the retrosplenial cortex (RSC) of mice. We then injected a cre-dependent form of the channelrhodopsin-2 variant ChETA carrying red fluorescent protein into the medial entorhinal cortex for labelling and optogenetic tagging of RSC-projecting layer Va cells. We specifically chose the RSC because of the extensive interconnectivity and close functional association between the RSC and the hippocampal-entorhinal circuit. We first confirmed the result of Surmeli et al that the main output from the MEC to the RSC comes from layer Va cells using conventional retrograde tracers and the modified AAV approach. We are currently in the process of tagging the cells for functional characterization. Preliminary results suggest that the layer Va cells do not fall into a single functional category and show low levels of spatial tuning.

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Poster

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Support: The Kavli foundation

Title: Patterned activity in the developing medial entorhinal cortex

Authors: *F. DONATO, H. OBENHAUS, R. I. JACOBSEN, M.-B. MOSER, E. I. MOSER
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Abstract: The medial entorhinal cortex (MEC) contains basic elements of the brain's representation of space. These include cell types whose firing is tuned to specific features of the environment (grid and border cells), or aspects of navigation (head direction and speed cells), and are anatomically intermingled in the MEC-L2 network. The most abundant cell type of this representation is the grid cell, which has hexagonally arranged firing fields that cover the entire available environment. Since no external stimulus occurs with a grid-like pattern, it is thought that the periodic firing of grid cells is formed by intrinsic network computations and, as such, should be influenced by local microcircuit connectivity.
Multiple models postulate that early network dynamics might be responsible for the emergence of regular grid firing. Correlated activity among groups of neurons during development might give rise to a continuous attractor network, where preferential connectivity among similarly tuned cells supports the regular firing of grid cells. Alternatively, grid firing could emerge at the end of a developmental learning phase as a single-cell process, resulting from Hebbian plasticity-dependent self-organization of multiple fields into a regular pattern. In support of both these hypotheses, and unlike other spatially modulated cells, the regular firing of grid cells emerges at the end of a protracted period during postnatal development, which coincides with the structural and functional maturation of the network.
We have shown that stellate cells in MEC provide an activity-dependent instructive signal that drives the structural maturation of the entorhinal-hippocampal network. However, the mechanisms regulating the functional development of the MEC and its possible influence on computation in grid cells are poorly understood. Here we investigate network dynamics in the developing MEC of awake, behaving mouse pups. By using ultrasound-guided injections of specific viral constructs in utero and immediately after birth, we have developed methods to (i) express genetically encoded calcium indicators in cohorts of cells characterized by the same birthdate or clonal origin and (ii) record network activity in such cohorts with a 2-photon

microscope. The results show widespread spontaneous activity in the developing MEC (P14-P35), with the emergence of clusters of correlated firing in the neural network, reminiscent of the early waves of correlated firing in the retina. We are currently determining if this early activity is instrumental in shaping network connectivity and properties of MEC-L2 in a way that might result in the emergence of regular firing in grid cells.

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Poster

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Title: Integrating time in lateral entorhinal cortex

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Abstract: The hippocampus has been identified as a critical structure for the formation of episodic memories, and receives the majority of its input from entorhinal cortex. While medial entorhinal cortex (MEC) has been shown to provide a spatial metric to hippocampus, lateral entorhinal cortex (LEC) has traditionally been thought to be the gateway through which nonspatial information enters the hippocampus. However, it is unlikely that LEC serves only as a conduit for nonspatial information, passing it onto the hippocampus without performing any computations. Thus, one would expect to observe some general overlying structure to the output that LEC sends to the hippocampus, akin to the spatial metric that MEC forms from the various movement-related inputs it receives. Studies up to now have observed LEC activity related to objects and task features, but have yet to reveal any such structure pointing towards the nature of computation in LEC. To look for a general structure of representation in LEC, we analyzed neural activity recorded across four experimental conditions: 1) free foraging in an environment with changing wall color, 2) free foraging in an environment where an object was intermittently present, 3) back-and-forth running on a circular track, 4) continuous alternation on a figure-eight

maze . Motivated by recent results demonstrating the utility of population-level approaches, we examined population activity in LEC. In the black/white and object experiments, we found very strong representation of environmental and temporal context. By contrast, in the circular maze and figure-eight experiments, we found reduced representation of temporal context, while in the figure-eight we also saw robust representation of behavioral context (turning left vs. right). The population-level representation of environmental as well as temporal context was generated primarily by cells exhibiting mixed selectivity integrating both selectivity for experiment-related features and time. Our results suggest that the computation LEC performs on its inputs varies depending on the animal's internal state. When the animal is free to explore, LEC continuously binds representations making up the animal's experience with the temporal context that it occurs in. When constraints are placed on the animal, either in terms of attention towards a goal or memory demands, the degree to which temporal context is encoded is significantly reduced, with LEC appearing to represent task-related features more strongly.

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Poster

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Title: Mixed selectivity in subiculum

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Abstract: The subiculum is one of the main output regions of the hippocampal formation. Together with CA1 it projects to a number of cortical and subcortical regions which rely on spatial and mnemonic information previously processed in the hippocampal formation. While the firing properties of CA1 place cells have been investigated quite extensively, our current knowledge of neuronal computations and representations in the subiculum remains very limited. In previous studies, Lever et al. (2009) have identified boundary vector cells in subiculum and

Olsen and Nitz (2017) reported that subicular neurons encode running direction on one-dimensional tracks. However, it is unknown whether cells with such properties form distinct functional populations or a single population with mixed selectivity. Furthermore, little is known about their distribution along the subiculum's proximodistal axis and across its layers. To address these questions, and to understand more what triggers firing in subicular cells we performed extracellular recordings of single units in the subiculum while rats performed an adapted version of the Pfeiffer & Foster task (2013). In this task, the rats alternate between random foraging and goal-directed running for chocolate milk rewards in a 6 x 6 array of food wells on an open arena. The recorded cells responded with varying degrees to behavioural features like proximity to wells, spatial location, heading angle and speed. The majority of cells showed mixed selectivity to two or more of those features and their relative feature preference varied. Furthermore, the cells' predominating feature response varied along the proximodistal axis of subiculum: strong modulation by proximity to food wells was most abundant in proximal subiculum (and the adjacent distal CA1) whereas strong responses to heading angle and speed were mostly found in the more distal subiculum (furthest away from dentate gyrus). It thus appears that the subicular output varies substantially along its proximodistal axis, and that the information provided is, in some respects, qualitatively different from the CA1 output.

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Poster

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Title: Spatial learning controls instinctive defensive behaviors in mice

Authors: *R. VALE[1,2], D. A. EVANS[1,2], T. BRANCO[1,2]
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Abstract: Animals often have to defend from predatory threats in dynamic settings that can change rapidly, and thus quickly adapting defensive strategies to match the current state of the environment is essential for survival. Although instinctive defensive behaviors are considered to be hard-wired stimulus-responses, little is known about how flexible mouse innate defensive behaviors are, and how fast they can be modified by experience. To address this, we investigated the dependence of escape behavior on learned knowledge about the spatial environment, and how the behavior is updated when the environment changes acutely. Using behavior assays, we first show that escape behavior in mice is a goal-directed action to reach safety: mice direct escape responses towards a shelter, even if this requires approaching the source of threat. Initiation of escape is preceded by a head rotation movement towards the location of the shelter, indicating knowledge of the spatial goal prior to flight start, and threat presentation while the animal is already in a safe area does not produce defensive behavior. We next demonstrate that navigation during flight does not rely on reaching local cues near the shelter, and that surprisingly, flight is terminated not upon reaching safety but after covering the distance between the animal's current position and the learned shelter location. The memory of shelter location in the environment can be formed in a single shelter visit lasting less than 20 seconds, and changes in shelter location are learned rapidly after a small number of trials. When the shelter is abruptly removed, mice quickly change their defensive strategies from flight to freezing. These findings demonstrate that instinctive defensive behaviors are controlled by very rapid and flexible spatial learning mechanisms, and we are currently preforming gain and loss-of-function experiments, together anatomical circuit tracing and in-vivo neural activity recordings to understand how spatial information is used by the midbrain circuits that control innate defensive behaviors.

Disclosures: R. Vale: None. **D.A. Evans:** None. **T. Branco:** None.

Poster

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Support: DFG grant SPP 1665

Title: Subicular neurons carry spatial information in high-frequency spikes

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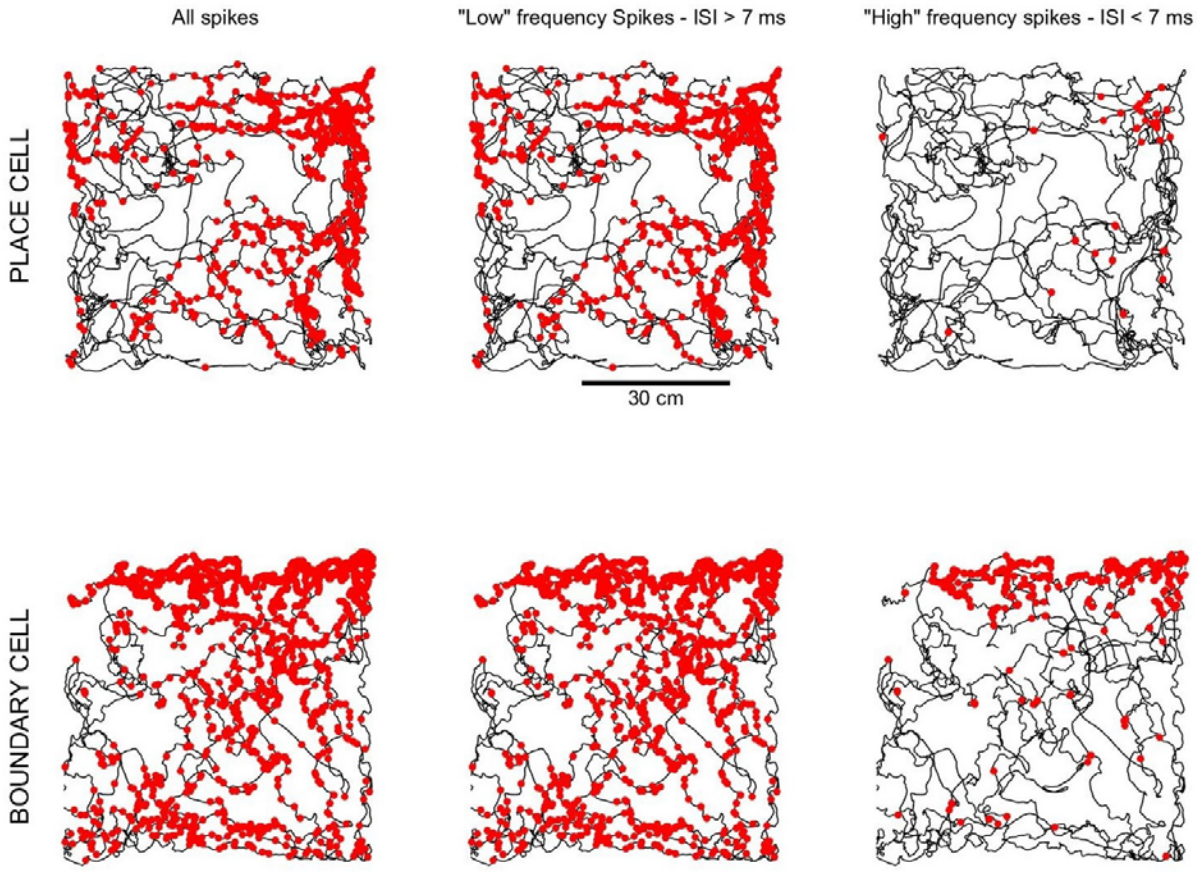
Abstract: The dorsal subiculum, a major hippocampal output relay, contains a high proportion of spatially tuned neurons, such as place cells or boundary cells. It is reciprocally connected to CA1, deep layers of entorhinal cortex or presubiculum but its role in the hippocampal circuit of

space coding and memory has not been clearly established. Slice physiology studies showed the presence of intrinsic bursting and regular spiking neurons in subiculum, and that appears to be correlated to the cell's proximo-distal position and postsynaptic targets.
Here, we ask how subicular spiking patterns are related to the encoding of spatial information. We used juxtacellularly obtained high-resolution recordings of spiking in freely moving male Long Evans rats (n = 19, age P40 to P120) foraging for food in a square open field arena (70 x 70 cm). We recorded the activity of subicular principal neurons (n = 38) and characterized the spatial tuning of 19 neurons for which at least 75 % of the environment was visited. Most of the cells provided rather small (median = 0.1907 bits/spike) but often significant ($p < 0.05$ for n=14 out of 19 cells) amounts of spatial information per spike. Cells with high firing rate tend to be less informative than less active cells (Spearman Correlation R = -0.6754; p = 0.0036). Spatial information was not correlated to the general bursting behavior of individual neurons (Spearman Correlation R = 0.3246, P = 0.1750). We found, however, that bursts and more generally groups of spikes occurring at high firing rate (> 80 Hz) provided more spatial information than single spikes occurring individually (median increase of 0.2578 bits/event; Wilcoxon signed rank test p = 0.0315). Thus, for several cells we observed clear place cell or boundary cell firing patterns for high-frequency spikes, whereas single spikes occurring individually lacked spatial tuning. We reason that subicular postsynaptic targets receiving information through facilitating synapses will be informed by high-frequency spikes and spatial discharges, whereas depressing synapses will transfer much less spatial information.



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Poster

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Title: Impaired spatial memory and enhanced habit memory in an animal model of post-traumatic stress disorder

Authors: *J. GOODMAN, C. MCINTYRE
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Abstract: High levels of emotional arousal impair cognitive memory mediated by the hippocampus and enhance habit memory mediated by the dorsolateral striatum (DLS). Several studies have suggested that the influence of stress on multiple memory systems may explain some of the behavioral and mnemonic symptoms of post-traumatic stress disorder (PTSD). However, the stress protocols employed in these previous studies differ considerably from a traumatic episode that produces PTSD-like symptoms. Thus, the present study examined whether single-prolonged stress (SPS; i.e. a protocol that produces PTSD-like symptoms in rats) influences multiple memory systems in a similar manner. Adult male Sprague-Dawley rats were subjected to SPS or no stress and, one week later, received training in one of two distinct plus-maze tasks. In the hippocampus-dependent place learning task, rats were reinforced to obtain food from a consistent spatial location. In the DLS-dependent response learning task, rats were reinforced to make a consistent body-turn response at the intersection of the maze to obtain food. SPS animals displayed impaired acquisition in the place learning task and enhanced acquisition in the response learning task, relative to non-stressed controls. In addition, during a subsequent extinction test in which food was removed from the maze, SPS rats demonstrated slower extinction in both tasks. The present findings are consistent with (1) prior observations indicating positive and negative effects of stress on DLS- and hippocampus-dependent memory, respectively, and (2) previous evidence demonstrating impairments in fear extinction following SPS. The influence of SPS on place and response learning in the present study may partially reflect memory function in individuals with PTSD and explain some of their symptoms.

Disclosures: **J. Goodman:** None. **C. McIntyre:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 084.26/SS25

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH083809

Title: Retrosplenial ensembles encode spatial and temporal context

Authors: *A. M. MILLER, A. C. SERRICHIO, A. L. TSE, C. SHI, D. M. SMITH
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Abstract: The retrosplenial cortex (RSC) plays a prominent role in learning and memory. The RSC is interconnected with the hippocampal formation and shares a number of functions with the hippocampus including spatial and contextual memory. In fMRI studies in humans, the RSC becomes active during many tasks that depend on context processing including spatial navigation, episodic memory, and recognizing context-specific objects. In rats, RSC lesions impair contextual fear memory and inhibitory avoidance memory, while optogenetic stimulation of the RSC can evoke a context-specific fear response. Despite this growing body of evidence for a role for the RSC in context processing, little is known about how the RSC represents contexts. In the closely related hippocampus, contexts are represented by the unique spatial firing patterns of many individual cells (i.e. place cells). However, RSC neurons do not exhibit highly specific place fields, and no studies have examined whether RSC neurons have distinct spatial firing patterns for different contexts. Therefore, to investigate RSC context processing, we recorded in the RSC of rats as they explored two square environments with unique wall colors, background colors, odors, and sounds. We found that the RSC clearly differentiated between the two spatial contexts. Spatial firing across the RSC population was more correlated between repeated visits to the same context than between visits to different contexts ($p < 0.01$, compared to shuffled data), consistent with the idea of context-specific spatial codes. The RSC population also contained a unique rate code for each context, such that population activity was more distinct during visits to different contexts than during two visits to the same context ($t(719) = 82.2$, $p < 0.001$). Interestingly, these representations occurred against a backdrop of "population drift," whereby the activity state of the RSC population steadily moved away from its starting state over the course of the recording session ($r = 0.62$, $p < 0.001$). This produced a unique rate code for each of the four ordered context visits, independent of their specific features ($F(2, 4339) = 208.5$, $p < 0.001$). These data are the first neurophysiological evidence that RSC ensembles encode the spatial and temporal context.

Disclosures: **A.M. Miller:** None. **A.C. Serrichio:** None. **A.L. Tse:** None. **C. Shi:** None. **D.M. Smith:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS061963

NIH Grant MH108837

Title: Retrosplenial cortex integrates long-range inhibitory CA1 inputs and excitatory thalamic inputs at layer 1 apical dendrites of layer 5 pyramidal neurons

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Abstract: Retrosplenial cortex is anatomically positioned to mediate communication between dorsal hippocampus and anterior thalamus, but the specific circuits that form the cellular basis for this interface are obscure. A long-range GABAergic projection has been described (Jinno et al., 2007; Miyashita and Rockland, 2007) that originates in dorsal CA1 interneurons and projects to layer 1 of retrosplenial cortex, but the postsynaptic targets have not been identified and the nature of synaptic transmission has not been assessed electrophysiologically. Using optogenetic-electrophysiological methods for analyzing long-range connections, we investigated how different presynaptic sources associated with dorsal hippocampal and thalamic networks converge on granular retrosplenial cortex (RSCg) neurons, focusing on pyramidal neurons in layer 5 that form intratelencephalic or pyramidal tract type projections. We found that these neurons are convergently innervated by inhibitory axons of non-fast spiking neurons in dorsal CA1, and excitatory axons of thalamocortical neurons in the anterior-ventral (AV) nucleus. In addition, these neurons received input from excitatory axons of burst-firing pyramidal neurons in subiculum (SUB). Analysis of the subcellular sites of innervation for each of these long-range inputs to layer 5 pyramidal neurons in RSC revealed that presynaptic axons from dorsal CA1 and AV inhibited and excited, respectively, the postsynaptic apical tuft dendrites in layer 1; in contrast, presynaptic SUB axons excited apical trunk and basal dendrites. Our findings delineate a unique circuit organization in which a focused excitatory thalamocortical projection is intersected by an inhibitory dorsal CA1 projection at the apical tufts of layer 5 pyramidal neurons. This circuit arrangement suggests a cellular basis whereby inhibitory signals from hippocampus regulate dendritic integration of excitatory signals from thalamus, modulating divergent output to downstream cortical and subcortical areas from RSCg.

Disclosures: N. Yamawaki: None. **J. Radulovic:** None. **G.M.G. Shepherd:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NIH R15 AREA Award 1R15AG045820¬01A1

Title: Maturation of excitatory synapses in the juvenile rodent hippocampus supports spatial navigation ability in the Barnes maze

Authors: *C. KIMBALL[1], J. CHEN[2], A. AGYEMAN-ANDOH[2], N. VALIBEIGI[2], D. G. MCHAIL[2], N. COSTELLO[2], T. C. DUMAS[3]
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Abstract: The hippocampus is a forebrain structure in mammals that has been shown to support navigation according to spatial context. Because spatial navigation ability comes online at postnatal day (P) 21 in rodents, investigating physiological differences in animals just under and just over P21 during maze exploration is a powerful tool to help determine which components of the system are sufficient to enable this complex cognitive skill. In prior work, we showed that pharmacological prolongation of AMPA receptor responses with AMPAKINE drug in animals under P21 elicited mature spontaneous alternation ability in a Y-maze. However, there is no explicit goal in spontaneous alternation. The Barnes maze, in addition to being a goal-oriented task, allows separate examination of learning and memory. It is also well suited to experiments with juvenile rats because it requires minimal time away from the dam, no food deprivation, can be completed within a short age range, and it is less stressful than the Morris Water Maze. In our recent work, we showed that animals under and over P21 learned to locate an escape hole in the Barnes maze. However, older animals learned the task more rapidly and displayed a more direct path to the goal during training and probe phases of the experiment. By delivering AMPAKINE drug to both age groups, the role of excitatory synaptic maturation in these different navigation strategies might be clarified. Preliminary results show that AMPAKINE delivery prior to training does not impact the learning curve during training. However, animals just over P21 given AMPAKINE drug before training show more direct goal approach than older control animals. Continued experiments will incorporate electrophysiological recording of hippocampal oscillatory activities and place cells during maze performance to elucidate network level effects of AMPAR maturation. Also, immunohistochemical assays will be performed to characterize AMPAR subunit composition in both age groups.

Disclosures: C. Kimball: None. **J. Chen:** None. **A. Agyeman-Andoh:** None. **N. Valibeigi:** None. **D.G. McHail:** None. **N. Costello:** None. **T.C. Dumas:** None.

Poster

084. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NSF CRCNS grant #1429937

ANR grant in France, entitled "A replay-driven model of spatial sequence learning in the Hippocampus-PFC network using reservoir computing"

Title: Complex rodent spatial navigation optimization in a large-scale environment

Authors: *B. HARLAND[1], M. CONTRERAS[1], P. SCLEIDOROVICH[2], M. LLOFRIU[2], N. CAZIN[3], A. WEITZENFELD[2], P. DOMINEY[3], J.-M. FELLOUS[1]
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Abstract: Everyday life often involves effective route planning in complex environments for both humans and animals. However, in the laboratory our understanding is still limited to simple spatial tasks, which usually consist of one or two goal locations and a limited number of navigation choices. One paradigm that combines dynamic planning, working memory, and spatial navigation is 'the Traveling Salesperson Problem' (TSP). The TSP is a classical artificial intelligence NP-hard problem that requires the subject to visit a fixed set of locations using the shortest possible path without re-visits. Our laboratory and others have shown that rats are able to quickly converge on near-optimal routes when performing a version of TSP in which they navigate for rewards in multiple cups (locations) in a small environment (150 cm diameter cylinder). The current work extends this line of research into a much larger environment (380 x 450 cm) allowing for more complex configurations in terms of distance between locations, as well as number of cups. Preliminary data suggests that rats are just as effective at converging onto near-optimal solutions in the large environment. Moreover, configurations with up to 9 cup locations were able to be optimized, whereas configurations with 11 cups produced comparatively less optimal, and less reliable paths. Additional work is underway to examine the neural substrates of spatial navigation optimization in the TSP by-way of recording spatially-tuned cells and oscillations in the hippocampus. Previously, we have shown that in the smaller environment dorsal hippocampal CA1 place fields during the task, and sharp wave ripple oscillations during post-task reconsolidation, may be associated with more optimal performance. As part of the ongoing work we explore whether ventral hippocampus, as well as dorsal, may be involved in facilitating optimal path planning when navigating in complex and large-scale environments.

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Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.01/SS29

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI JP17K17668

JSPS KAKENHI JP16K16071

JSPS KAKENHI JP25242002

Title: A variation of the method of constant stimuli: A new psychophysical method and its numerical and experimental evaluation

Authors: ***K.-I. SAWAI**[1], Y. SATO[1], K. AIHARA[1], Y. NAKAJIMA[2]
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Abstract: We propose a psychophysical method that can be an alternative to the method of constant stimuli, which is one of the most common psychophysical methods. Comparison stimuli are chosen so that they divide a certain range of a stimulus continuum into short equal segments. Each comparison stimulus is presented only once, and thus as many comparison stimuli as the number of the total trials can be used. The employment of such finely distributed comparison stimuli is the point of our method in contrast to the existing method, in which comparison stimuli are sparse and each of them is repeated many times in an experiment. The comparison stimuli of our method can provide the detailed structure of the psychometric function. Computer simulations showed that our method is useful when the slope of the psychometric function is extremely steep, and also when the psychometric function has an unusual shape, e.g. such that the underlying perceptual distribution is a bimodal Gaussian mixture. We conducted a psychophysical experiment to validate our method. The results and their implications are also discussed.

Disclosures: **K. Sawai:** None. **Y. Sato:** None. **K. Aihara:** None. **Y. Nakajima:** None.

Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.02/SS30

Topic: H.02. Human Cognition and Behavior

Title: Tracking the relationship between eye movements and surveys

Authors: *J. BUENROSTRO[1], M. F. AWAD[2], D. L. LARRANAGA[5], J. F. AWAD[3], T. GORJI[4], R. MORALES[2], S. A. DREW[2]
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Abstract: Asthenopia, also known as visual discomfort, is a condition associated with near work tasks (e.g. reading). Visual discomfort is a relevant issue in student populations due to the high frequency of reading throughout one's academic career. Symptoms include blurred vision, double vision, and oculomotor fatigue relating to the accommodative and vergence systems. Two validated surveys have been developed, the Visual Discomfort Survey (Conlon et al. 1999) and the Convergence Insufficiency Symptom Survey (Borsting et al. 2003), that assess subjective reports of chronic symptoms associated with visual discomfort and are found to be associated with accommodative insufficiency and convergence insufficiency, respectively. However, these measurements rely on patient reports of perceived symptoms experienced. The present work endeavors to explore the relationship between subjective reports and objective observations of asthenopic symptoms by utilizing an EyeLink 1000 Plus eye tracking system in conjunction with the aforementioned surveys. It was hypothesized self-reported symptom behaviors such as higher blink rates and re-reading would be reflected in the recordings of participants' eyes during a 10 minute reading task Preliminary results suggest a moderate relationship between observed and reported rereading rates, indicating that participant's self-reported rereading rates may be accurate predictors of their observed rereading. However, the present data does not appear to indicate that there is a significant relationship between survey scores and blink rate, and further investigation is warranted. Given the high rate of need for practitioners to consider the accuracy of symptom self report measures, this study is of great importance to better understanding the neurological system's contribution to eye movement and accommodation.

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Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.03/SS31

Topic: H.02. Human Cognition and Behavior

Support: IBS-R015-D1

Title: Effect of predictability on the reconstruction of dynamic visual objects in early visual cortex

Authors: *S. PARK[1], H. SONG[1,2], W. M. SHIM[1,2]
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Abstract: Previous work showed that features interpolated during apparent motion (AM) are represented in the population-level feature tuning responses in primary visual cortex, which indicates that the human brain fills in details that are absent in raw sensory inputs but are reconstructed during dynamic object transformations via top-down processes (Chong, Familiar, & Shim, 2016). Predictive coding accounts hypothesize that feedback can suppress responses in early sensory cortex when incoming sensory information is predicted by top-down expectations. However, it remains unclear how top-down, filled-in neural representations in early visual cortex are also modulated by the predictability of the sensory input. Here, using fMRI and encoding methods, we examined how neural representations of interpolated features during dynamic filling-in are affected by the predictability of the moving object's trajectory. On each block, a gabor patch that was oriented radially to the central fixation point, was sequentially presented in each quadrant to induce rotational AM along the circular trajectory. AM was either predictable, where the gabor appears to move only in one direction (clockwise or counterclockwise) during a block, or unpredictable, where the direction of its motion appears to randomly change. Consistent with the previous finding, regions in V1 retinotopically mapped to the AM path showed feature-selective responses for orientation interpolated during AM, and such responses were more pronounced in the beginning of the AM sequence and decreased as AM repeated. Crucially, feature responses were stronger when the trajectory of AM was unpredictable, compared to when it was predictable. Our results show that the neural representations of dynamically interpolated features are more robust when they are less predictable by top-down expectations. Our finding is consistent with the predictive coding hypothesis, and suggests that top-down representations of filled-in features in early visual cortex can be suppressed via feedback when the uncertainty of the upcoming sensory input is low.

Disclosures: S. Park: None. **H. Song:** None. **W.M. Shim:** None.

Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.04/SS32

Topic: H.02. Human Cognition and Behavior

Title: The effects of tDCS on orientation discrimination task performance

Authors: A. BIN DAWOOD[1], A. DICKINSON[2], A. AYTEMUR[1], C. HOWARTH[1], E. MILNE[1], *M. JONES[1]
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Abstract: Cortical excitation-inhibition (E-I) balance plays a critical role in cognition and behavior and has been hypothesized to underlie neurodevelopmental disorders such as epilepsy and autism. In the case of Autistic Spectrum Conditions (ASC) differences in E-I balance ratio have been inferred from performance of psychophysical tasks such as the visual Orientation Discrimination Task (ODT). A superior performance of ODT in ASC is thought to be due to increased levels of inhibition in the occipital cortex but studies linking ODT to E-I balance are equivocal. Thus, the current study investigates the putative association between ODT performance and occipital E-I balance by manipulating E-I balance using transcranial Direct Current Stimulation (tDCS). tDCS is a non-invasive brain-stimulation technique that modulates neural excitability: Anodal-tDCS increases excitability, while Cathodal-tDCS increases neural inhibition. 19 neurotypical human participants completed two tDCS-ODT sessions. In each session, participants received 10-minutes ‘off-line’ occipital tDCS (1st session: Sham, 2nd session: Anode or Cathode, 2mA) followed by the ODT. Orientation discrimination thresholds were measured using a two alternative forced choice adaptive staircase procedure. Stimuli were presented on a LCD monitor 52 cm from the participant. On each trial a reference grating and a target grating were presented sequentially. Participants were asked to judge whether the target grating has been rotated clockwise or anti-clockwise compared to the reference grating using left and right arrow keys on a keyboard. For oblique ODT performance there was a significant increase in performance following Cathodal tDCS and but no difference following anodal TDCs. As such, this data provides some further evidence that higher neural inhibition may be related to superior performance of the ODT.

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Poster

085. Perception and Imagery

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.05/SS33

Topic: H.02. Human Cognition and Behavior

Title: Malformations of the human corpus callosum compromise low-level visual perception

Authors: *A. S. MAALLO[1,2], R. J. DEAN[1], L. J. RICHARDS[1,3], M. BARTH[4], J. B. MATTINGLEY[1,5], G. J. GOODHILL[1,2]
[1]Queensland Brain Inst., [2]Sch. of Mathematics and Physics, [3]Sch. of Biomed. Sci., [4]Ctr. for Advanced Imaging, [5]Sch. of Psychology, Univ. of Queensland, Brisbane, Australia

Abstract: People with congenital agenesis of the corpus callosum (ACC) do not normally display the cognitive deficits typically observed in "split-brain" patients, in whom the corpus callosum has been surgically cut to control generalized seizures. Therefore, ACC is an interesting model for how the brain compensates for altered brain development and wiring. Individuals with ACC have been shown to perform within the normal range even for tasks requiring interhemispheric communication, such as bilateral matching of letters, colours, and shapes. Other work, however, has identified conditions under which ACC individuals perform poorly, such as bilateral pattern matching. Here we compared visual perception for pairs of stimuli of different types, presented bilaterally across the two visual fields, or unilaterally within the left or right visual field alone, in a small group of ACC participants and in controls. During the behavioral tasks, we measured the response accuracy and latencies to unilaterally and bilaterally presented letters (familiar information) and Gabor patches (unfamiliar, low-level information). We also tested performance in spatial matching across hemifields. In controls, there were no significant differences in performance between unilateral and bilateral presentations across any stimulus type. They also had quick and accurate responses to the bilateral spatial matching task. In the ACC individuals, we observed three patterns of performance, in which the individual showed either: (i) significantly decreased accuracy and/or longer response times in tasks requiring interhemispheric communication, (ii) chance accuracy when responding to unfamiliar low-level stimuli, but not to familiar letter stimuli, for both unilateral and bilateral presentations; or (iii) performance similar to controls. Our results suggest heterogeneity in visual processing deficits in the congenitally acallosal brain. We are currently conducting fMRI and diffusion-weighted imaging experiments with the same individuals to investigate the neural correlates of these behavioral effects.

Disclosures: A.S. Maallo: None. **R.J. Dean:** None. **L.J. Richards:** None. **M. Barth:** None. **J.B. Mattingley:** None. **G.J. Goodhill:** None.

Poster

085. Perception and Imagery

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.06/SS34

Topic: H.02. Human Cognition and Behavior

Support: IBS-R015-D1

Title: Attention-controlled temporal frequency sensitivities in human striate and extrastriate visual cortex

Authors: *I. KIM[1,2], D. KIM[1,2], W. SHIM[1,2]
[1]Ctr. For Neurosci. Imaging Research, IBS, Suwon, Korea, Republic of; [2]Biomed. Engin., Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Temporal frequency tuning in human visual cortex, including early and intermediate visual areas, has been extensively examined (Fox & Raichle, 1984; Kastner et al., 2004; Singh, Smith & Greenlee, 2000). However, in previous studies, the effect of temporal frequency may have been confounded by differences in the level of attention, as stimuli varying at different temporal rates induce differences in perceptual salience. Furthermore, temporal frequency dependent neural modulations along the human visual stream, including high frequency ranging up to 30 Hz, are not fully revealed. Using fMRI, the present study investigated temporal frequency dependent neural response of the lateral geniculate nucleus (LGN), primary visual cortex (V1), and extrastriate areas (V2, V3, V3A, V4v, and V5/MT) while controlling for the effect of attention. To control for the level of attention in response to each stimulus, subjects monitored a fixation for occasional color changes while viewing a contrast-reversing checkerboard flickering at 0.5, 2, 6, 20, or 30Hz. Neural activities in V1, V2 and V3 were modulated as a function of the stimulus flicker rate such that the response amplitude increased from 0.5 to 6 Hz and decreased thereafter, indicating a low pass filter up to 20 Hz in early visual cortex. Even after excluding stimulus-driven attentional effects, temporal frequency sensitivities in early visual cortex measured in BOLD responses were consistent with previous PET and electrophysiology results in human and non-human primates (Fox & Raichle, 1984; Hawken, Shapley & Grosof, 1996). Moreover, the LGN showed reduced but similar temporal frequency dependent modulation. In contrast to prior studies which reported temporal frequency sensitivities in extrastriate areas, no significant frequency dependent modulations were found in V3A, V4v and V5/MT. Our findings indicate robust temporal frequency dependent neural modulations in early visual cortex in the frequency range between 0.5 and 30 Hz and suggest distinct ranges of temporal frequency tuning for early and extrastriate visual areas.

Disclosures: I. Kim: None. **D. Kim:** None. **W. Shim:** None.

Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.07/SS35

Topic: H.02. Human Cognition and Behavior

Title: Frontopolar transcranial direct current stimulation changes intrinsic functional connectivity networks during resting-state fMRI

Authors: *J. AHN[1], ***J. AHN**[1], *J. AHN[2], J. HAN[2], M. KANG[3,4], S. HAN[1,2]
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Abstract: The frontopolar prefrontal cortex (FPC) has been implicated in complex, high order cognitive functions. There are, however, no studies that have evaluated the effects of transcranial direct current stimulation (tDCS) targeting the FPC. tDCS has largely been proposed to modulate brain cognitive functions in a non-invasive way. The current study investigates whether both tDCS electrodes arrangement on the FPC would induce changes in functional connectivity of FPC-based intrinsic networks measured by functional magnetic resonance imaging (fMRI). We further aim to explore whether frontopolar tDCS can result in changes of default mode network (DMN). Twenty healthy subjects participated in the study and resting-state brain connectivity data were collected before and after tDCS with fMRI. tDCS was applied for 15 min at 0.5mA with the anode electrode placed over FP1 and the cathode over FP2 according to the 10-20 international system for EEG. Relatively small electrodes (12.5 cm^2) compared to conventional ones (35 cm^2) were used in order to constrain electric field induced by tDCS exclusively to the FPC. The left FPC was first selected as a seed region of interest (ROI) for resting-state functional connectivity analysis. Spherical FPC mask of 10mm radius was created surrounding center MNI coordinate [-21.5 70.2 -0.1] of 10-20 cortical projection points of FP1. Furthermore, the posterior cingulate cortex (PCC) was selected as another a priori ROI to investigate whether focal tDCS on the FPC altered DMN. Spherical mask of the left PCC was created whose center MNI coordinates [-3 -54 27] was determined based on previous resting-state studies. Time series of every voxel was then extracted and functional connectivity between each voxel and seed regions were calculated. The paired t-test results showed significant decrease of functional connectivity between the left FPC and ipsilateral hippocampus, contralateral dorsolateral prefrontal cortex and medial frontal cortex after tDCS. In contrast, the left FPC and bilateral precuneus, supramarginal gyrus and contralateral anterior cingulate cortex were functionally more connected after applying tDCS. Furthermore, functional link of the left PCC with the bilateral precuneus decreased whereas link with the bilateral hippocampus was enhanced after tDCS. In addition, regional homogeneity (ReHo) analysis found decreased ReHo in the bilateral insula whereas enhanced ReHo in the bilateral medial temporal regions was observed after tDCS. These results show that

frontopolar tDCS induces modulation of distinct intrinsic functional connectivity networks including the subcortical regions of the human brain.

Disclosures: **J. Ahn:** None. **J. Han:** None. **M. Kang:** None. **S. Han:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: 1-DP5-OD021352-01

NIH T32 NS 043126

Title: Systems-level network integration predicts trialwise TMS effects on temporal perception

Authors: ***R. WURZMAN**[1], M. WIENER[3], R. H. HAMILTON[1], H. B. COSLETT[1], J. D. MEDAGLIA[2]
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Abstract: Predicting TMS effects before stimulation occurs may clarify the nature of TMS effects in clinical and experimental settings and provide opportunities in personalized therapeutics. TMS effects occur within complex distributed brain networks, and techniques that adequately represent network complexity may provide predictive value. To test this possibility, we examined system level states to predict individuals' perception of time duration. We administered brief trains of TMS while healthy human participants (n=19) performed a temporal discrimination task and concurrently recorded electroencephalography (EEG). On different days, TMS pulse-trains were administered to either a control site or the right supramarginal gyrus (rSMG), a region implicated in encoding time perception. We used dynamic community detection to identify major functional systems across 32 EEG electrodes and identified functional coherence patterns associated with temporal similarity perception prior to the pulse (pre-pulse), and after the pulse but before the stimulus (post-pulse). We found that increased frontotemporal-somatomotor integration during encoding was associated with an increase in the perceived duration of the stimulus on a trialwise basis (generalized mixed linear model, fixed effect = -1.38 0.57, *p=0.016*). This relationship was reversed for the control site, with increased frontotemporal-somatomotor integration during encoding associated with longer perceived stimulus durations (fixed effect = 1.87 0.68, *p=0.005*). In addition, we found that electrodes Fz and FC2 switched affiliation from the right frontotemporal community to the somatomotor community following rSMG stimulation. In contrast, after mid-occipital control stimulation,

somatomotor and centrally located electrodes shifted community assignments, revealing a community organization encompassing the parietal-occipital area. The changes in SMA community affiliation following rSMG stimulation is consistent with the SMA's role as a pacemaker in temporal encoding. Together, these results suggest that the difference in the relationship between frontotemporal-somatomotor system integration and trialwise temporal perception for the two stimulation sites is driven at least in part by changes in macroscopic community structure as well as shifts in specific electrodes' community affiliation. These findings constitute a step towards closing the loop between brain state, measurable behavior, and non-invasive brain stimulation, which could unlock the capacity for personalized TMS-based therapeutics.

Disclosures: R. Wurzman: None. **M. Wiener:** None. **R.H. Hamilton:** None. **H.B. Coslett:** None. **J.D. Medaglia:** None.

Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.09/SS37

Topic: H.02. Human Cognition and Behavior

Support: R01 EY023384

Title: The spatial and spectral distribution of visual information: An unbiased exploration using electrocorticographic recordings in the human brain

Authors: *Z. SABRA[1], ***Z. SABRA**[1], L. BONILHA[2], T. NASELARIS[1]
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Abstract: Visual information encoded in field-potential signals is both spatially and spectrally distributed. The exact forms of the spatial and spectral distributions, and their dependence on stimulus content, attentional state, and brain area are still being actively explored. In the current study we explored the spatial and spectral distribution of visual information using a large sample of electrocorticographical (ECoG) activity from 17 patients. Patients enrolled in our study were asked to fixate on a screen presenting 450 images of three object categories (faces, buildings, and cars), while varying their attention to each category. This experimental design resulted in nine distinct pairings of attended and perceived object category. Recording channels were distributed across prefrontal, parietal, temporal and occipital cortical lobes. For all of the roughly 1450 ECoG channels in this study, we calculated condition-specific power spectral density (PSD) functions that revealed the distribution of power across frequency bands for each combination of attended/perceived object category. We noted two prominent patterns of variation: broadband variations in power, and narrowband variations that were restricted to low (<30Hz) frequencies.

To quantify the relative importance of these spectral patterns, we applied principal component analysis (PCA) to the condition-specific PSDs. For each subject, PCA was applied to pooled data from all channels. Thus, the principal components (PCs) coupled variation across experimental conditions with variation across the brain. Consistently across all 17 subjects, the first PC revealed by this analysis reflected a broadband variation in power that accounted for about 15% of total spectral variation. The second through fourth PC were also quite consistent across subjects, revealing distinct peaks at sub-gamma frequencies and accounting for another 15% of spectral variation, collectively. We then fit channel-wise encoding models that predicted variation along the first through fourth PCs as a function of stimulus condition. For the broadband-like PC1, cross-validated encoding model accuracy was highest for channels in ventral temporal cortex, and less significant for channels in the rest of the brain. For the narrowband-like PCs two, three and four, encoding model accuracy was broadly distributed across both temporal and prefrontal cortices. Our unbiased description of a large sample of ECoG signals thus emphasizes the importance of two distinct spatial and spectral encoding patterns: narrowly distributed broadband encoding, and widely distributed low-frequency narrowband encoding.

Disclosures: **Z. Sabra:** None. **L. Bonilha:** None. **T. Naselaris:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: Intramural Research Program of the NIH, NIDDK

Title: Differences between onset and sustained rivalry bias are explained by the canonical cortical circuit model

Authors: C. HOUGHTON[1], *C. C. CHOW[2], S. VATTIKUTI[1]
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Abstract: Perceptual rivalry is the competition between conscious interpretations (percepts) of a static stimulus. Many psychophysical phenomena are explained by a simple canonical cortical circuit model[1] including static and intermittent rivalry, normalization, disambiguation, short-term memory, and decision-making. Empirical results comparing onset to sustained rivalry have been posed as a challenge to rivalry models since there are differences in percept bias statistics[2]. Prior work showed that a mutual inhibition model can explain some of these differences[3]. Here we show that the same canonical cortical circuit model with identical parameters quantitatively matches previously published onset and sustained statistics, while matching other rivalry

constraints.
1: Vattikuti S, Thangaraj P, Xie HW, Gotts SJ, Martin A, Chow CC. CanonicalCortical Circuit Model Explains Rivalry, Intermittent Rivalry, and RivalryMemory. PLoS Comput Biol. 2016 May 3;12(5):e1004903. doi: 10.1371/journal.pcbi.1004903.
2: Stanley J, Forte JD, Cavanagh P, Carter O. Onset rivalry: the initialdominance phase is independent of ongoing perceptual alternations. Front HumNeurosci. 2011 Dec 5;5:140. doi: 10.3389/fnhum.2011.00140.
3: Shpiro A, Rinzel J, Rubin N. Percept strength at the onset of bistable perception. BMC Neuroscience 2010 11 (Suppl 1):P37. doi: 10.1186/1471-2202-11-S1-P37

Disclosures: C. Houghton: None. **C.C. Chow:** None. **S. Vattikuti:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

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Thousand Youth Talents Plan Y4HX072006

Hundred Talent Program Y3CX022003

Title: Frontal neural oscillatory activity modulates bistable perception switch

Authors: *C. QIN[1,2], Y. PAN[1,2], Z. TAN[1,2], W. ZHOU[3], L. REN[4], L. WANG[1,2]
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Abstract: Subjective perception alternates spontaneously between different interpretations when faced with ambiguous sensory inputs. Such multistable perception phenomena have been utilized as an important approach to investigate neural dynamics of consciousness. Previous studies have proposed that the fronto-parietal network may modulate perceptual switch, but recent studies suggest that the induced frontal activity may be related to executive function occurring during behavioral reaction. Despite rigorous investigations, the underlying neural mechanisms of

multistable perception remain elusive. This study used intracranial electroencephalography (iEEG) to explore neural dynamics during bistable perception switch. Epileptic patients with implanted depth electrodes performed a structure from motion (SFM) task to judge the rotation direction of a ball perceived. Patients constantly need to report their perception state in self-pace via keyboard buttons. We found that Beta (13-20Hz) oscillation significantly decreased and high-gamma (70-150Hz) activity significantly increased in the dorsal LPFC (dLPFC) , and increased high-gamma activity was observed in the ventral LPFC (vLPFC). Both changed activities appeared 400ms before switching action. Moreover, such frontal electrodes did not showed significant activities during the maintenance of one perceptual state. In addition, electrodes in the motor cortex indeed showed significantly increased high-gamma activity around the action time. ROC analysis between switch and non-switch action did reveal significant difference, which precluded the potential effect of simple execution function. Comparison with a replay condition in which an unambiguous half ball was presented showed weaker activity in the dLPFC area and almost no activity in the vLPFC. The Beta activity pattern in the dLPFC may support for the hypothesis that changed Beta oscillation indicated the disruption of the current state. These results suggest a dissociative role of VLPFC in subjective perception fluctuation that may rely on concordant information transmission between the dLPFC and vLPFC.

Disclosures: C. Qin: None. **Y. Pan:** None. **Z. Tan:** None. **W. Zhou:** None. **L. Ren:** None. **L. Wang:** None.

Poster

085. Perception and Imagery

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Program#/Poster#: 085.12/SS40

Topic: H.02. Human Cognition and Behavior

Support: NIH R01EY024161

Title: Evidence for face selectivity in early vision

Authors: *F. CAMPANA[1], J. MARTIN[2], L. BOKERIA[3], S. THORPE[2], M. RIESENHUBER[3]
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Abstract: Humans are remarkably accurate and fast at detecting objects (e.g. an animal, a vehicle) in natural, cluttered, with above-chance manual responses starting as early as 250 ms post-stimulus onset. Recently, the use of saccadic response paradigms revealed that object categorization can be achieved even faster than previously thought, with the fastest saccades toward faces starting as early as “express saccades”, the fastest known saccades in humans, that

are directed toward luminous dots (Crouzet et al., 2010. Furthermore, the ultra-fast saccades toward face targets are spatially very precise. Together, the high precision of the saccades and their very short latencies suggest the hypothesis that early visual areas might contain face-selective representations. V1/V2 especially is a good candidate, with small receptive fields subtending as little as 1° in humans at 7° eccentricity, and responses measured over central parieto-occipital starting between 45 and 60 ms in human subjects. In the present study, we tested this hypothesis in humans by displaying especially small faces (2° height) in a series of experiments. In two eye tracking experiments, we investigated the visual features sufficient to elicit ultra-fast saccades toward faces displayed at 7° eccentricity. In an fMRI and an EEG experiment, we investigated the locus and latency of the earliest differential neural responses to upright vs. inverted faces displayed at 7° eccentricity. The use of small faces in periphery maximized our chance to activate “face detectors” in V1/V2. Due to the selectivity of V1/V2 to low-level features, the more the compared categories differ at the level of their low-level features (e.g. faces vs. houses), the more a differential response in V1/V2 will reflect responses driven by those low-level differences rather than category selective responses. The use of upright and inverted faces here thus constitutes a very stringent test of category selectivity. Those experiments brought converging evidence that faces elicit specific responses in V1 around 40 ms post-stimulus onset. This very early selectivity was found in the right hemisphere, for left hemifield presentations of the stimuli specifically, while selective responses to faces started later in the case of right hemifield presentations. Our findings suggest a revision of the traditional “simple-to-complex” model of visual hierarchical processing in which object-selective representations are only found in high levels, to a model in which early areas can contain neuronal representations for complex objects that allow the fast localization of objects with high ecological importance.

Disclosures: F. Campana: None. **J. Martin:** None. **L. Bokeria:** None. **S. Thorpe:** None. **M. Riesenhuber:** None.

Poster

085. Perception and Imagery

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Program#/Poster#: 085.13/SS41

Topic: H.02. Human Cognition and Behavior

Title: Visual scanpaths during the visualization of self and other faces

Authors: *I. B. GREBOT, W. C. DE SOUZA, M. A. G. FEITOSA
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Abstract: The face is our main path for communication. It allows us to extract vital information to social interaction. How face recognition happens has been an object of great interest to

researchers of several fields. One aspect of face recognition is how familiar a face is to us. Although there is strong evidence for holistic processing of faces, studies have shown diferences in the processing of familiar and unfamiliar faces. This research aimed to investigate the existence of a pattern in the visual scanpath of faces in different degrees of familiarity. In order to achieve this, the eye-tracking methodology was used to compare familiar, unfamiliar and self faces of university students during a free viewing task. Results were analyzed by measuring the Levenshtein distance between categories, using the Needleman-Wunsch algorithm. When analyzing the first four fixations, a great similarity was observed between the three categories. However, when comparing the sequences, self faces were shown to have little similarity to the other two categories.

Disclosures: I.B. Grebot: None. **W.C. De Souza:** None. **M.A.G. Feitosa:** None.

Poster

085. Perception and Imagery

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Support: National Science Foundation Grant SBE-0542013

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Title: Visual imagery of objects of expertise in face-selective visual areas

Authors: *M. A. SUNDAY[1], R. W. MCGUGIN[1], B. J. TAMBER-ROSENAU[2], I. GAUTHIER[1]
[1]Dept. of Psychology, Vanderbilt Univ., Nashville, TN; [2]Dept. of Psychology, Univ. of Houston, Houston, TX

Abstract: Studies have shown that visual imagery, defined colloquially as “seeing in the mind’s eye,” can be characterized as a top-down reinstatement of visual perception. We investigated if this extends to domains of visual expertise. Using functional MRI, a tool uniquely suited to investigate intrinsic processes like mental imagery, we asked if the fusiform face area was involved when car experts mentally imagined cars. Results from the multi-voxel pattern analysis provided evidence that representations of imagined cars did, in fact, differ from imagined common objects in face-selective visual areas of car experts. Furthermore, we found evidence that object categories are similarly represented during both mental imagery and perception since a pattern classifier trained on imagery data was able to classify data acquired during perception.

Thus, our results lend support to the idea that visual imagery mirrors perception, not only in early visual areas, but also further down the visual processing stream.

Disclosures: M.A. Sunday: None. **R.W. McGugin:** None. **B.J. Tamber-Rosenau:** None. **I. Gauthier:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: KHIDI Grant HI15C3175

NRF Grant 2016R1C1B2010726

Title: Representations of emotional scenes during perception and memory retrieval

Authors: *D. PARK[1], S. LEE[1,2]
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Abstract: Perception and retrieval of emotional scenes are essential for human survival in the real world. For example, retrieval of scenes with negative emotions allows us to predict and deal with harmful situations. Prior studies have reported that emotional arousal influences and modulates encoding and consolidation processes of memory. Then, how are emotional scenes represented in the brain compared to neutral scenes during perception and retrieval? To address this, here we performed an event-related functional magnetic resonance imaging (fMRI) experiment. Prior to scanning, participants were asked to memorize fixed parings of 10 auditory cues (pseudoword) and scene images (5 negative and 5 neutral scenes). Every participant showed good performance (>99% correct) in the forced-choice tests after training, indicating accurate retrieval of scene information. In addition, the subjective vividness rating showed comparable scores between retrieved negative scenes and neutral scenes. During scanning, participants passively viewed the scene images or recalled the images in response to the auditory cues in the absence of any visual presentation. Using multi-voxel pattern analysis and whole brain searchlight analysis, we found that negative scene perception and retrieval engaged broader neural networks in the brain compared to neutral scene processes. Moreover, there was stronger decoding of scene information in frontal areas and weak decoding in occipital areas during negative scene retrieval whereas the opposite pattern was observed during neutral scene retrieval. Furthermore, the structure of the representations between frontal and visual areas was more similar in emotional scene perception than neutral scene perception. These results suggest that

more top-down signals are integrated into the processes of perception and retrieval of negative scenes compared to neutral scenes.

Disclosures: D. Park: None. **S. Lee:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: NSF Grant BCS-1431147

Title: Neural habituation, novelty detection, and the visual perception of words: an ERP study

Authors: *H. PIRES DE LIMA JACOB, D. E. HUBER
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Abstract: The neural response to a briefly viewed stimulus can blend with the response to a subsequent stimulus. However, if the first stimulus is shown for a longer duration, the degree of blending is reduced, resulting in enhanced novelty detection. At the same time, if the subsequent stimulus is identical, the observer may fail to identify that a repeat occurred (‘repetition blindness’). Huber and O’Reilly (2003) proposed that neural habituation underlies this temporal parsing, explaining both novelty detection and repetition blindness. As applied to visual word identification, short duration prime words blended with subsequent words, producing a priming advantage, whereas long duration prime words produced a priming deficit. This describes the pattern for repetition priming of the target, but the opposite occurred when the prime was identical to the incorrect choice in the final forced choice display. Neural predictions of this habituation model were previously confirmed by examining ERPs to the target word. However, that study did not address perceptual decision making and novelty detection because it was impossible to separate the ERP responses to the two simultaneously presented choice words. The present study used a modified version of the task, presenting a single test word for a same/different judgment after the briefly flashed target word. In keeping with the prior target-ERP results, the test-word-ERP N170 was smaller when the test word was a repetition of a long duration prime as compared to a test word that differed from the prime, with this effect occurring regardless of whether the test word matched the target. Furthermore, these effects were absent following a short duration prime. This pattern was predicted by the neural habituation model using default parameters based on a prior application of the model to behavioral data. In addition, there was a robust N400, but only when the test word differed from both the prime and the target. This was explained by the model with the inclusion of a ‘novelty detection’

representation. These results provide additional support for the theory that neural habituation exists to allow temporal parsing and novelty detection.

Disclosures: H. Pires De Lima Jacob: None. **D.E. Huber:** None.

Poster

085. Perception and Imagery

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US National Science Foundation (BCS1358907)

China Scholarship Council (CSC)

Title: Probing the electrophysiology of visual word form processing and connections to language areas using intracranial recordings in humans

Authors: *N. REN[1,2], A. RAUSCHECKER[3], O. RACCAH[2], J. PARVIZI[2], B. A. WANDELL[4]
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Abstract: The neural mechanisms underlying reading have been extensively studied using psychophysical and fMRI methods. However, the timing of neural responses as stimulus information passes through the brain's reading network is not well understood. To understand the temporal dynamics of brain activity during visual word form processing, we recorded intracranial EEG signals from 5 epilepsy patients implanted with subdural electrodes while the patients viewed different types of word form stimuli. Stimuli comprised real words, pseudowords, consonant strings, partially phase-scrambled words and completely phase-scrambled words. We presented words in the central, ipsilateral, and contralateral visual fields. During stimulus presentation, patients were instructed either to judge the fixation dot color ("incidental reading") or to decide whether or not the stimulus was a real word ("lexical decision"). We used the power and time of onset of high-frequency broadband (HFB, 70-170Hz) signal as a measure for the level of cortical activation and its onset. As expected, the left visual word form area (VWFA) response amplitudes did not differ between real words, pseudowords, or consonant strings, but all of these responses were significantly larger than responses to phase-

scrambled images. VWFA responses to words in the ipsilateral visual field were delayed compared to responses to words in the contralateral or central visual field. In one patient we obtained simultaneous recordings from the VWFA as well as putative Broca's and Wernicke's areas. The response onset latency difference between words in the contralateral and ipsilateral visual fields was also present in these language areas. In two patients who performed both the incidental and lexical decision tasks, the maximum response amplitude of the left VWFA to words was prolonged in the lexical decision task, most likely due to sustained engagement of the VWFA with the language circuitry required for the lexical decision. These data provide information about the timing of electrophysiological responses to words in the VWFA and in other language areas, which will lead to a deeper understanding of the neural mechanisms of reading.

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Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DC004263

NIH Grant EY024858

Title: Competition for event formation in auditory scene analysis

Authors: H. TANG[1], *E. S. SUSSMAN[2]
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Abstract: The study of temporal integration and how sequential sound elements are grouped into meaningful percepts has been within the focus of researchers for decades. The current study addressed the question of how within-stream temporal integration occurs in the context of a complex sound environment. The ability to identify specific events within complex mixture of sounds depends upon multiple processes: the overall segregation of sounds to streams and the within-stream integration of sound elements to perceptual units. The current study tested the hypothesis that competition plays a role in event-formation when there are multiple overlapping sound sources, and assessed whether attention could override biases set up by stimulus-driven factors. Two conditions were used, one in which competition was set up by similar rising tone patterns occurring in a high and a low stream, and another in which the competition was

removed by using dissimilar standard patterns in each frequency stream. In one session, participants watched a movie and had no task with the sounds and in another session they attended to specific within-stream events. The mismatch negativity (MMN) component of event-related brain potentials, which can be evoked when sounds are attended or unattended, was used to index event formation. When the standard patterns were similar, and participants were instructed to ignore the sounds, MMNs were elicited by deviants in only one of the frequency streams: detection of the other was obscured. In contrast, when the standard patterns were different, MMNs were elicited by deviants in both streams. This suggests that the similarity of melodic patterns between the two streams induced competition for deviance detection. This limitation of automatic processing was resolved when participants were instructed to attend to the similar sound patterns, and detect the sound deviants. That is, MMNs were elicited by deviants in both streams when the target was the deviant event that was missed (no MMN) when the sounds were ignored. In the condition that did not share similar melodic patterns, in which there was no cross-stream competition, attention did not affect MMN elicitation in either stream. Results were similar as when the sounds were ignored. Together, these results support the hypothesis that attention redistributes processing resources to resolve competition coming from different sound streams in noisy environments.

Disclosures: **H. Tang:** None. **E.S. Sussman:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: HU intramural funding

Title: Synesthetic perception of speech: Why Hungarians like Spanish and Chinese marvel at French

Authors: *I. GRANTYN
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Abstract: In Cognitive Science synesthesia is considered as a rare phenomenon. In some cases it is associated with neurologic disorders (autism, epilepsy) and outstanding linguistic or counting faculties (Savant syndrome). The aim of the present study is to clarify whether synesthetic perception also occurs among healthy adults. It will be shown that that semantically concrete words acquired in an early stage of L1-acquisition are particularly prone to be subject of heteromodal sensory perception. The study consists of two complementary parts: i) the SAE-Test (Sensory Adequacy Evaluation-test), which includes 108 items from 6 languages, Indo-European

vs. non-Indo-European, agglutinative vs. non-agglutinative, 3 word classes, and ii) the VI-Test (Voice Influence-Test), which comprises 18 nonwords with different degrees of phonetical variation. The first part verifies, if and to what extent a test person (TP) is capable to judge the sensory fitting of a word/speech chain to the encoded concept, using a scale from 0-10 and two sensory dimensions - visual (dark/light) and tactile (soft/hard). The second part explores the auditory fitness of a TP using a discrimination task of enchained speech sounds. 106 TP were recruited according to the 6 stimuli languages: German, English, French, Spanish, Hungarian, and Turkish. An additional cohort of TP included speakers of Mandarin, a tonal language. Both tests were performed twice with an interval of several weeks in order to check the consistence of the TP decisions made during the first trial. An initial series of experiments (40 TP) revealed that the TPs were able to judge the adequacy of the presented stimuli and to associate non-auditive sensory features such as soft/hard. The question remained as to whether these decisions were determined by cultural imprint during language acquisition, rather than linguistic universals. Approaching the 'Nature vs. Nurture' debate, it was interesting and surprising to compare the results of the Indo-European and Non-Indo-European native speakers. The Hungarian TP group assessed consistently rather low adequacy values to the stimuli of their own language concerning the sound-concept relation. The same came out for the Turkish and Chinese TP. Also with regard to the 'favorite' items, the decision making followed clear patterns, Spanish words being regarded as the most adequate auditory representations. It could be tentatively concluded that the widely established hypothesis of linguistic arbitrarity, which postulates the absence of iconic relations between sign and referent (e.g. the word *horse* and the horse itself) does not comprise the whole lexicon.

Disclosures: I. Grantyn: None.

Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.20/SS48

Topic: H.02. Human Cognition and Behavior

Title: Differing neural strategies in left and right-handed individuals during motor imagery

Authors: T. T. WHITTIER[1], J. MIZELLE[2], *N. MURRAY[2]
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Abstract: The areas of the cortex that are involved in voluntary movement are also activated during the imagination of movement, a process known as motor imagery (MI). Implicit motor imagery involves mental simulation of biological motion in order to solve task parameters, and to internally represent an observed action for understanding. The hand laterality judgment (HLJ) task has commonly been used to study implicit MI, and evokes activation of the sensorimotor

areas used in MI. The HLJ task involves presentation of left- and right-hand images in different orientations and postures to participants. The participant task is to identify the laterality of the stimulus hand image. Brain-imaging studies of HLJ have generally shown a strong contralateral activation in the prefrontal and premotor regions relative to the stimulus hand, with a greater response to images matching the dominant hand. However, there is a lack of research to determine if left-hand dominant individuals show this same pattern. Recent work has shown that left-handers have more bilateral activation while completing a similar task, regardless of the handedness of the stimulus. The purpose of this study was to identify any differences in brain activation between right and left-handed individuals as they executed a HLJ task requiring implicit motor imagery. 24 young healthy adults (12 right hand dominant, 12 left hand dominant) participated in the study and completed a protocol using the HLJ task with simultaneous EEG acquisition from a 64-channel cap. Participants were presented with a series of 240 images divided into four blocks randomly chosen from a bank of 544 images. Each image showed a hand in a posture identified as simple (flat hand or fist), recognizable (e.g. point with index finger, thumbs up), or unique (no previous mental association) and rotated in increments of 45 degrees. Following a stimulus presentation, participants responded by button press to identify each stimulus as a right or left hand as fast and as accurately as possible. Based on event related potentials, results showed that left-handers activated the premotor region on both sides more than right-handers and that right-handers showed a greater activation of the inferior parietal area than left-handers when completing the HLJ task. These results suggest a difference in the areas of the brain relied upon to solve motor related tasks that require implicit motor imagery. Further, our findings highlight the importance of better understanding basic neurobiological differences between right- and left-dominant individuals in motor control.

Disclosures: **T.T. Whittier:** None. **J. Mizelle:** None. **N. Murray:** None.

Poster

085. Perception and Imagery

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI 16K12440

Title: Role of the precentral cortex for kinesthetic motor imagery: fMRI multivariate decoding of finger movements

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Abstract: Although it is well accepted that kinesthetic motor imagery activates the motor-related areas of higher order, the role of the precentral cortex for motor imagery is unclear. This study aims to test the hypothesis that the motor imagery recruits the similar neural representational geometry with those by motor execution in the precentral cortex. Using fMRI with multi-voxel pattern analysis (MVPA), we tried to classify the content of motor imagery with the brain activations based on those of execution. Ten normal right-handed adults executed or imagined the tapping one of the right fingers. In one test block, one finger to be moved or imagined to move was indicated by one of four Japanese characters, which appeared over the center fixation point on the screen. Then the number was displayed below the fixation point and countdown from 12 to one for one second each, and subjects were requested to execute or imagine 12 repetitive movements with one's required finger synchronized with the displayed number. The participants underwent a total of 8 sessions (4 each for execution and imagery conditions), with each session comprising 12 blocks. The electromyography (EMG) was placed over the hypothenar, extensor digitorum communis, extensor indicis proprius, and flexor digitorum superficialis muscles of the both hands. The separate localizer scan, during which the participants repeatedly opened and squeezed their right hand 12 times during the task blocks, was conducted to identify each participant's precentral cortex related to finger movement. We then used MVPA to decode which finger the subjects were imagining to move using the classifier developed by brain activation during execution condition. EMG analysis showed that participants made no movement during imagination. The averaged activities of the precentral cortex showed significant increase during execution, while those during imagery were comparable to baseline activities during rest. The results of MVPA showed that we could correctly classify the content of motor imagery using the activities of the left precentral cortex evoked by actual movements (averaged accuracy rate = 35.2%; chance-level of 25%). In addition, the content of motor imagery together with modality (execution or imagery) was successfully classified with the left precentral cortex activities (averaged accuracy rate = 27.3%; chance-level of 12.5%). Whereas the correct decoding of modality indicates that execution and imagery have distinct neural representations, the successful classification of fingers across modality indicates that the motor imagery has a similar representational geometry with execution in the precentral cortex.

Disclosures: K. Ogawa: None. **F. Imai:** None. **J. Shinozaki:** None. **H. Saito:** None. **H. Nagahama:** None. **Y. Sakurai:** None. **T. Nagamine:** None.

Poster

085. Perception and Imagery

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 085.22/SS50

Topic: H.02. Human Cognition and Behavior

Support: European Union's Horizon 2020 Research and Innovation Programme No 645553

Title: Combining computational modeling and brain imaging reveals distinct processing of different movement qualities

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Abstract: Can we, by the understanding of movement and the analysis of its quality, translate movement into e.g. sounds (sonification)? This could be of interest since it would provide the possibility to help e.g. blind persons to "see" (experience) a dance choreography, but also to gain a deeper understanding of human perception of rhythmic movements. But how can properties of movement be translated to sounds in an objective and relatable way? For this purpose we have developed a computational model able to segment dance movements into multi-layer features based on low level physical signals from e.g. motion capturing. To be able to validate and improve this model, we first need to understand how a healthy individual perceives dance and its respective aesthetic properties for which we designed an fMRI experiment. We asked several dancers to perform two aspects of dance called "Fragility" and "Lightness" that have been identified by the computational model as being very different in the feature space. Fragility has been defined as: *"A sequence of non-rhythmical upper body cracks and leg releases. It emerges, for example, when moving at the boundary between balance and fall, resulting in short movements with continuous interruption of motor plans. The resulting movement is non-predictable, interrupted, and uncertain*", whereas lightness can be defined as: "*A series of body movements that are smooth, fluid and elegant and therefore result in predictable, continuous and certain movement"*. In total, 10 dancers have been recorded on video resulting in 120 ~10sec videos. MRI data were acquired in the Maastricht Brain Imaging Center, Maastricht University (Netherlands), with a 3T MAGNETOM Prisma fit scanner (Siemens, Erlangen, Germany). Anatomical and functional data were acquired based on protocols from the Human Connectome Project (HCP, https://www.humanconnectome.org/), but adjusted for the scanner used (fMRI: TR=1.33s, voxel size=2mm^3, multi-band factor=3). Anatomical and functional images were processed by the pipelines available from the HCP. We used SPM routines to test for differences in voxel level brain activations between the two dance conditions. The contrast Fragility>Lightness revealed stronger activation in inferior parietal, supra-marginal and central sulcus regions, which are well known to be related to action observation. Conversely, the Lightness>Fragility contrast showed greater activation for Lightness in inferior parietal, precentral sulcus and superior parietal regions. Our results represent a promising step towards understanding the objective characteristics of movement on which aesthetic perception builds.

Disclosures: **M. Vaessen:** None. **E. Abassi:** None. **A. Camurri:** None. **B. de Gelder:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: FRM Postdoctoral Fellowship

ANR

Title: Sensing the world through a hand-held tool

Authors: *L. E. MILLER[1], L. MONTRONI[1], R. SALEMME[1], V. HAYWARD[2], A. FARNÈ[1]
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Abstract: In the seventeenth century, Descartes famously discussed a blind man's ability to actively navigate his environment with a cane. Still, almost four centuries later, we have very limited knowledge of what environmental properties can be sensed with a tool (e.g., Yamamoto & Kitazawa, 2001) and how tools gate meaningful sensory information to the user (e.g., Emerson & Rodgers, 2005). Further, all previous studies have treated a tool as an intermediary between the user and the environment, and not as a sensory surface in and of itself. By combining psychophysics and contact mechanics, we show that a tool communicates sensory representations of object impact location to the user's hand with previously unexpected accuracy. In three psychophysics experiments, we find that human participants can localize where an object contacts a hand-held rod with high spatial resolution. This is true for conditions of both active tool wielding as well as passive stimulation, demonstrating that both sensory and motor variables play important roles in perceptual object localization. Given the structural dynamics of rods, we reasoned that this ability reflects perceptual mechanisms that are highly sensitive to location information encoded in the tool's natural modal response to impacts. By leveraging multivariate methods that are commonly used to characterize neural representations, we find that tools mechanically transduce object location into a vibratory codes upon impact. The structure of these vibratory input motifs are consistent across trials and emerge within ~20 ms. Thus, the vibratory response of a rod constitutes a meaningful pre-neuronal transformation that can be exploited by the nervous system during perception, a finding that has parallels in the rat whisking system (e.g., Bagdasarian, et al., 2013). We further find that location information is encoded in the higher frequencies of the modal response, suggesting that location information could be rapidly and precisely transduced into neural signals by afferents in the hand. In sum, our results demonstrate that a hand-held tool functions as an extended sensory apparatus, letting the user sense the location of objects beyond the boundaries their physical body.

Disclosures: **L.E. Miller:** None. **L. Montroni:** None. **R. Salemme:** None. **V. Hayward:** None. **A. Farnè:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS084948

Title: Leveraging a motor task to reveal intermediate cognitive states

Authors: *S. D. MCDOUGLE, J. A. TAYLOR
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Abstract: Mental rotation is the classic example of an hypothesized analog cognitive computation. When humans make similarity judgments about two rotated objects, reaction time (RT) is linearly predicted by the objects' relative degree of rotation, suggesting a kind of "analog" rotation of a mental percept. To date, evidence for such analog computations has been indirect, in the form of RT measures in psychophysical tasks or modulations of BOLD signals in fMRI. Here, we set out to find direct evidence of a form of mental rotation in action. We reasoned that if the mental rotation operation is interrupted, "intermediate" states should be revealed. We accomplished this by leveraging a simple reaching task, which allowed us to track the progression of mental rotation rendered in overt behavior.
Subjects (n = 32) performed two tasks: The first was designed to verify the signature of mental rotation, the second to interrupt mental rotation and "read out" intermediate rotational states. In the FREE task, subjects performed pairs of trials: In the first trial of the pair (learning trial), subjects reached to a target and observed cursor feedback that was rotated with a particular sign and magnitude. In the second trial of the pair (execution trial), subjects were instructed to counteract the previously experienced rotation to make the cursor terminate on the target. As hypothesized, RT was linearly predicted by subjects' reach angles. The FORCED task was a forced-response time task: The task required that subjects initiate their reaches after target appearance but before the last of four equally-spaced tones. Cursor feedback was perturbed by a consistent 90° rotation. Importantly, the time of target appearance was titrated such that subjects had a variable window to process the target location, compute the solution, and initiate their movement. Thus, subjects had to react rapidly, presumably in the middle of mental rotation. Under these conditions, subjects predictably executed movements directed at intermediate locations between the target and goal, providing a readout of a cognitive computation in action. The observation of such intermediate states has general implications for the nature of analog

computations and mental imagery, and specific implications for the neural mechanisms behind the cognitive control of reaching movements.

Disclosures: S.D. McDougle: None. **J.A. Taylor:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: nsf award # 1631820

Title: Connectivity analysis during self-contemplating image formation

Authors: *D. GUPTA[1], Q. MENG[2], E. HONG[3], F.-S. CHOA[4]
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Abstract: Many accumulated evidences have shown that the conscious brain can activate and change circuits in the subconscious brain. It is possible that conscious brain may go through higher level brain nodes to indirectly interact with lower level subconscious circuits. For example, meditation has shown significantly influence to people's mind states and some of them actually benefit the health of their bodies. It would be interesting and highly beneficial to understand the mechanisms employed by such activity to achieve these effects. Here, we study the trends or pattern in the functional connectivity of different regions of brain using purely mind operations and imagination. Subjects were asked to form math operations, emotional and motor function related images in their minds with eyes closed. Using a trigger, subject marked time stamp indicating completion of image formation in mind. EEG data within 1000 milliseconds before the task completion marker was taken and processed using the sliding window approach. First, the EEG data was preprocessed by filtering (for delta, theta, alpha and beta wave) followed by removal of artifacts. Then, sliding window approach was used where data points within a time window of 100ms were taken to calculate correlation among all pairs of electrodes for one window. The window is then shifted in time by 10 ms of data points that overlaps between the successive windows. This process results in quantification of the time-varying behavior of the chosen metric over the duration of the scan. We observed high standard deviation ($\sigma \sim 0.87$-0.95) among highly fluctuating correlation values for delta wave and relatively lower deviation ($\sigma \sim 0.55$-0.75) for that of beta wave activity. Fluctuating correlation values for neurons with theta and alpha wave activity mostly deviated as $\sigma \sim 0.73$ or so. This reflects that neuron oscillations associated with beta wave activity are highly correlated and in phase than that in delta wave. In

other words, this strongly suggests that beta wave activity is involved with locking neurons together thereby playing a critical utility role for information query. Moreover, we found that for delta wave, mostly anterior frontal lobe and the occipital lobe associated with visual cortex were highly out and in phase with each other. Combining this with our earlier studies, we also found that theta waves indicated high out and in phase interaction between the regions located at the edge of the cortex involving lateral temporal regions, frontal lobe and posterior occipital lobe. To conclude, we identified and summarized prominent functional connectivity states and patterns with imagnation.

Disclosures: D. Gupta: None. **Q. Meng:** None. **E. Hong:** None. **F. Choa:** None.

Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: Chinese program of introducing talents to Universities (111 Project, No. B08020)

Shanghai Jiao Tong University (YG2016ZD06, 14JCRZ05）

Title: Electro-neurophysiological change in traditional buddhist meditation

Authors: *S. TONG[1], X. GUO[1], X. WANG[1], M. WANG[1], Z. WANG[1], T. XUE[2], H. LI[2], T. XU[2], B. HE[3], D. CUI[2]
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Abstract: Meditation originated from Indian Ayurvedic system of medicine and has been developed as a Buddhist tradition for thousands of years. Most meditation studies have been focusing on modern mindfulness. However, little has been known about the traditional Buddhist meditation and its influences on brain plasticity. In this study, we recruited 73 Tibetan Buddhist practitioners with more than 5 years of mediation experience, including 22 Nyingma, 14 Shechen, and 37 Gelug practitioners, as well as 31 meditation-naive Tibetan controls from the local region with matched culture and living background. Sixty-four channel EEG signals were recorded during the resting and meditation states, respectively. Topographies of scalp EEG in each of rhythmic band over one min were compared between different states, between Buddhist practitioners and meditation-naive Tibetan, as well between practitioners in different sects. We found that the beta and gamma power were significantly increased in Buddhist practitioners from the resting to meditation states (resting vs meditation, beta: $F(1,62)=8.854$, $p=0.004$; gamma: $F(1,62)=6.250$, $p=0.015$), with manifestation in the bilateral frontal area in Nyingma and

Shechen practitioners, or the right frontal lobe in Gelug practitioners. While in resting state, Buddhist practitioners showed increased delta power in the central and parietal areas compared with the meditation-naive controls (practitioners vs controls, $F(1,93)=5.376$, $p=0.023$), especially significant for Nyingma and Shechen practitioners. These electrophysiological differences between practitioners and controls suggest a long-term (i.e. resting state) and short-term (meditation vs resting) brain plasticity in meditation practitioners. And interestingly, such differences showed the relevance with the religious sect.

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Poster

085. Perception and Imagery

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Program#/Poster#: 085.27/SS55

Topic: H.02. Human Cognition and Behavior

Title: Detecting meditative states through meta-state matching with time-varying functional connectivity matrices

Authors: *S. HIWA, T. HIROYASU
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Abstract: Objective Recent studies have revealed that meditation strengthens self-awareness, attention control and emotion regulation. Now it has been one of the best ways to promote our well-being. However, it is often difficult for early-stage practitioners to know how well they can meditate. The objective of our study is to develop the algorithm to quantify how meditative we are from time-varying brain activities measured by neuroimaging methods.
Materials A novice group of 20 healthy adults (23.0 +/- 2.6 years; 6 females) with no experience of meditation and an expert group of 2 healthy male adults (37.0 +/- 0 years) experienced more than 1000 hours of Vipassana Buddhist meditation participated in this study. They were asked to perform breath-counting meditation for 5 min in the 1.5T MRI scanner. Pre- and post-meditation resting states (5 and 10 min) were also scanned continuously.
Methods We defined a 'meta-state' of the meditating brain and evaluated the distance between the current state and the meta-state. Dynamic functional connectivity was calculated for the mean BOLD time courses of 116 regions defined by automated anatomical labeling through a sliding-window approach. The functional connectivity matrix at each time point was thresholded and binarized. The averaged matrix of the meditation block was calculated for each expert data, and their logical conjunction was used as the meta-state. The ratio of meta-state occurrence was defined as the number of common non-zero elements between the meta-state and the matrix at each time point, divided by the total number of non-zero elements of the meta-state. It was

compared between the two subject groups.
Results Graph theoretical analysis of the meta-state revealed that the right precentral gyrus, the right middle frontal gyrus, the right inferior parietal lobule and the bilateral supramarginal gyrus were the hub regions during meditation, because they showed the highest betweenness centrality among the 116 brain regions. They have been shown to be key regions in meditation in recent studies. The ratio of meta-state occurrence of the experts increased from the rest block to the meditation block and then decreased in the last rest block, while that of the novices has no consistency between the individuals. The average ratio of meta-state occurrence during the meditation was 90.0+/-2.9% for the experts and 72.3+/-7.8% for the novices. These results suggested that the expert meditators controlled their brain activities through meditation.
Conclusion It was suggested that our proposed method could detect the meditative state and also evaluate the quality of meditation. The method will support our daily practice of meditation.

Disclosures: S. Hiwa: None. **T. Hiroyasu:** None.

Poster

085. Perception and Imagery

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Program#/Poster#: 085.28/SS56

Topic: H.02. Human Cognition and Behavior

Title: Network analysis of brain activity during breath-counting meditation by fNIRS

Authors: *S. YAMAMOTO[1], S. HIWA[2], T. HIROYASU[3]
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Abstract: Introduction: Attention deviates from the focused task, and the state that is not related to the task is called mind wandering. About 50% in daily life, people are in a state of mind wandering. Mind wandering is said to lead to a decrease in happiness and work efficiency. Mindfulness meditation is drawing attention. Mindfulness is to pay attention to what is happening now, and effects of stress reduction and concentration are expected by mindfulness meditation. In this study, brain states during breath-counting meditation were compared with meditation novices, and the degree of functional brain network was compared. In the experiments, brain function measurement was performed using functional Near Infrared Spectroscopy (fNIRS).
Methods: The meditation task is breath-counting which counts entrance and exit of breathing. Six male meditation beginners participated in the experiment. Brain activity at rest and breath-counting was measured using fNIRS (ETG - 7100). The measurement site was 116 channels in the forehead, crown and occipital area. The measured data was processed by a band pass filter with a frequency of 0.008 Hz to 0.09 Hz. All the channels were correlated by stochastic

registration with the sites divided by Automated Anatomical Labeling (AAL). The correlation coefficient matrix between all channels with the correlation of the channel's blood flow change was calculated at rest and breath-counting, respectively. The order of degree corresponding to an edge density of 15% was compared to rest and breath-counting.
Results, Discussion: At breath counting time compared to rest before pre-task, it was found that the order of the coupling of the middle prefrontal cortex increased in many subjects. The middle prefrontal cortex is reported to be a brain part that acts during meditation and controls attention. The results suggest that the brain part of attention control emphasizes with other regions during meditation. Also, at the time of rest after breath-counting, the degree of coupling of the middle frontal round remained high. This result indicates that the brain state during meditation was preserved even after meditation. It is a new result that brain states at the time of rest and pre-task rest were different.
Conclusion: A comparison of the order of the degree of resting time and meditating in a novice was performed. Brain activity was measured by fNIRS. When breath-counting was performed, the order of the degree of the medial frontal gyrus increased compared to that at rest. Therefore, even if a meditate novice, there is a possibility that the brain part of attention control exaggerates with other regions more than at rest.

Disclosures: S. Yamamoto: None. **S. Hiwa:** None. **T. Hiroyasu:** None.

Poster

085. Perception and Imagery

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Title: Precuneus Delta Power as a potential marker of unconsciousness under anesthesia

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Abstract: Background: Increased electroencephalogram (EEG) delta power may be a marker of unconsciousness but recent data from the isolated forearm technique suggests that consciousness is possible under anesthesia with profound increases in frontal delta (and alpha) power. Herein we hypothesized that differences in posterior cortical delta power would discriminate disconnected consciousness (ketamine-induced unresponsiveness) from unconsciousness (propofol-induced unresponsiveness). Methods: Six and nine human subjects underwent ketamine or propofol sedation to unresponsiveness respectively while recording high density EEG (64-channel and 256-channel respectively) in two separate experiments. Wake versus drug

contrasts of the spontaneous EEG were made for delta (0.5-4Hz; primary outcome) and other EEG bands in sensor and source space. The change in EEG activity induced by a drug was then contrasted using drug data normalized by the corresponding wake data. Data are reported using False Discovery Rate (FDR) correction of multiple comparisons. Results: Ketamine increased gamma power (28-40Hz; FDR $p<0.05$), but not power in the other bands, over the scalp compared to wake though source changes were not detected (FDR $p>0.05$). In contrast, propofol increased power in all bands, in sensor and source space (FDR $p<0.05$). The peak difference in the delta band was in the precuneus. In source space, occipital alpha power and temporal and inferior frontal gamma power was higher for wake than propofol (FDR $p<0.05$). The contrast of change in EEG activity induced by ketamine compared to propofol, demonstrated a widespread increase in delta power with propofol (sensor and source space; FDR $p<0.05$), with a peak effect in the precuneus. Compared to ketamine, propofol also increased frontal theta, alpha and beta power, while ketamine increased widespread gamma and occipital theta (FDR $p<0.05$). Conclusions: In the light of the recent data, these data suggest precuneus delta power may be a marker of consciousness under anesthesia.

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Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: supported by Nissan Motor Co., Ltd.

Title: Neural correlates of ambient thermal discomfort: an fMRI study

Authors: *K. D. SANTOS KAWATA[1], S. YAMAZAKI[1], K. HIRANO[1], Y. HAMAMOTO[1], H. OI[5], A. KANNO[2], R. KAWASHIMA[3], M. SUGIURA[1,4]
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Abstract: Despite the increasing interest in the psychological process underlying the environmental thermal perception (i.e., sensation and comfort), its neural correlates have been poorly investigated. We have recently made a first attempt to address this issue using an fMRI and custom-made MRI-compatible equipment (Oi et al., submitted). Although we identified the neural response to the sensation (cold > hot) in the insula and dorsal striatum, we failed at identifying the neural correlates of thermal comfort. The current study followed this up using

improved experimental settings and analysis. Participants were 46 healthy young adults. As in our previous study, each subject was covered by a large plastic canopy fitted to the size of the MRI gantry, 10 minutes heating and 10 minutes cooling of the inside air alternated twice. The range of manipulation spanned between uncomfortably cold and hot (average 20-27 °C) with a comfortable range in between, which allowed us to dissociate the effects of thermal comfort from those of thermal sensation. All subjects were asked to independently rate their subjective levels of thermal sensation and comfort using four-grade rating every 30 sec. The neural responses correlated with these two types of rating were determined. Major updates of the research design from the previous one included the encouragement of subjects' sensitive rating (i.e., to rate 1 or 4) and exclusion of the subjects who did not rate 1 or 4 for each measures from the analysis, which resulted in the number of analyzed subjects 33 and 30 for the sensation and comfort, respectively. A significant correlation of activation with thermal sensation was identified positively in the left somatosensory cortex and negatively in the right dorsal striatum. A significant negative correlation with thermal comfort was identified in the right precuneus and posterior cingulate cortex. The findings on the thermal sensation were consistent with our previous study and other studies using a local thermal stimulation. We have now successfully identified the neural correlates of thermal comfort in terms of the response to the discomfort perception. Given potential involvement of these medial parietal regions in the self-focused thinking to avoid negative experience as previously suggested, the findings may reflect the behavioral-planning process in response to adverse environmental perception.

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Poster

085. Perception and Imagery

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Topic: H.02. Human Cognition and Behavior

Support: NIH/NIDCD Grant DC013122

Title: Alpha power response-relevant and response-irrelevant distractors with clear and vocoded speech in a delayed match-to-sample task

Authors: *E. AUER, JR, S. P. EBERHARDT, L. E. BERNSTEIN
Dept. of Speech, Language, and Hearing Sci., George Washington Univ., Washington, DC

Abstract: Accurate speech perception often involves attending to information in the context of irrelevant or relevant distracting information. Alpha power is typically modulated when attentional demands change. Alpha power was measured in EEG recordings obtained while participants carried out four tasks, in which every trial comprised three temporal intervals, and the stimuli were consonant-vowel nonsense syllables that were either natural speech recordings or sinewave vocoded speech. Nineteen normal-hearing participants attended to a memory stimulus in Interval 1 and made a speeded decision to a probe in Interval 3. For three of the tasks, a speeded *match versus mismatch* decision was made regarding the Interval-1 and -3 stimuli. Across tasks, Interval 2 presented one of the following; (1) Irrelevant distracters (IDs); (2) Relevant distractors (RD), for which a detection response was required following the match/mismatch response, as well as irrelevant distracters; or (3) No distracters (ND). The fourth task was a baseline (B) control task, for which the participant passively received Intervals 1 and 2 and responded *upward* or *downward* to a tone glide in Interval 3. Tasks were in separate blocks. EEG recordings were made throughout the paradigm. Alpha power (8-12Hz) was extracted during Interval 2 using an FFT transform in EEGLab and averaged over 250-ms epochs from pre-to-post stimulus (-500 to +500ms). Linear mixed models showed that alpha power was significantly modulated bilaterally over temporo-parietal and right frontal electrodes as a function of memory task and speech stimulus type. Speech stimulus type and task interacted such that relevant and irrelevant distractors resulted in larger differences in alpha modulation with the natural compared with the vocoded speech, suggesting that alpha modulation is sensitive to clarity of speech information in distractors.

Disclosures: E. Auer: None. **S.P. Eberhardt:** None. **L.E. Bernstein:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

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Topic: H.02. Human Cognition and Behavior

Support: Alzheimer’s Disease Neuroimaging Initiative (ADNI)

Title: The effects of brain volume on the learning and forgetting of the serial position components of a multi-trial word list in mild cognitive impairment and Alzheimer's disease

Authors: *J. W. GRIFFIN[1], S. E. JOHN[2], B. E. GAVETT[1]
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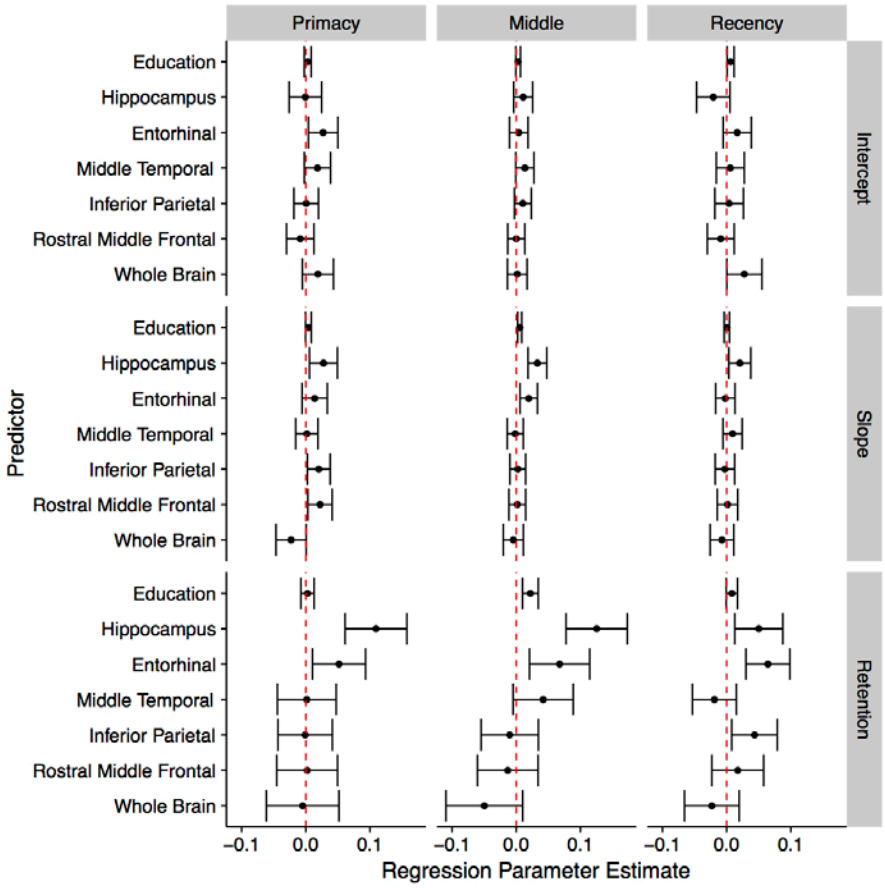
Abstract: We conducted this study to better characterize the degree to which list learning brain-behavior relationships can be identified in mild cognitive impairment (MCI), Alzheimer’s

disease (AD), and normal controls. Specifically, we utilized latent growth curve structural equation modeling to examine the relationship between medial temporal and other brain volume measurements and primacy, middle, and recency intercepts and slopes in a large, heterogeneous sample (N = 819) acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI). This is the first known study to statistically model the relationship between structural neuroanatomy and Auditory Verbal Learning Test performance using a multivariate model incorporating serial position and latent variables for list learning intercepts, slopes, and percent retention. Our hypothesized model showed good model fit, robust CFI = 0.950, robust RMSEA = 0.047, 95% CI [0.042, 0.051]. We found strong associations between latent variables and entorhinal cortex, hippocampus, rostral middle frontal gyrus, and inferior parietal lobule volumes. A multiple groups analysis revealed that latent intercepts and slopes differed by diagnostic group. This suggests that brain volume abnormalities associated with typical AD pathology, such as medial temporal lobe atrophy, are differentially related to list recall based on serial position. Entorhinal cortex was strongly associated with primacy intercept, whereas only education and whole brain volume were associated with recency intercept. Furthermore, entorhinal cortex and hippocampus were strongly associated with primacy and recency slopes, and percent retention for all serial positions. Rostral middle frontal gyrus and inferior parietal lobule were only associated with primacy slope. These results show that serial position latent intercepts and slopes are differentially affected by variability in brain volumes, and that these associations lead to different patterns of recall across diagnostic groups.



Disclosures: **J.W. Griffin:** None. **S.E. John:** None. **B.E. Gavett:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.02/SS61

Topic: H.02. Human Cognition and Behavior

Title: Object and scene memory are differentially associated with CSF markers of Alzheimer's disease and MRI volumetry

Authors: *D. BERRON[1,2], H. SCHUETZE[1], A. CARDENAS-BLANCO[1,2], K. FLIESSBACH[9,3], M. WAGNER[9,3], A. SPOTTKE[3], M. REUTER[3,10,11], S. TEIPEL[12,4], K. BÜRGER[13,5], A. SCHNEIDER[3,9], O. H. PETERS[14,6], P. NESTOR[2], J. PRILLER[15,6], J. WILTFANG[16,7], C. LASKE[17,8], F. JESSEN[18,3], E. DÜZEL[1,2,19]
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Abstract: Alzheimer's Disease (AD) is characterized by progressive tau-pathology in perirhinal and entorhinal cortices (ErC), hippocampus, parahippocampal cortex and the retrosplenial/posterior cingulate region (RS/PCC). The latter also shows early amyloid plaque accumulation. While these regions form a network for complex objects-in-scene memories, there is a segregation of object memory into a perirhinal-entorhinal and scene-layout memory into a RS/PCC-parahippocampal-entorhinal pathway. Here we investigated whether complex objects-in-scene memory, as opposed to isolated object or scene-layout memory is correlated with CSF levels of Aß42 and phospho-tau and MR volume and thickness measures. 204 participants (cognitively healthy, subjective memory complaints, mild cognitive impairment or early AD) of

the DELCODE study of the DZNE performed a complex scene recognition memory task. CSF samples were available from 80 participants. 78 participants also performed a second task on mnemonic discrimination of objects (in the absence of scenes) or scenes (in the absence of objects). Of these 28 CSF samples were available. MR thickness measures were obtained from T1 and T2-weighted images using Freesurfer 6. Objects-in-scene recognition memory correlated with right and left PCC volume, right and left hippocampal volume, Aß42, phospho-tau and their ratio. Isolated object and scene discrimination correlated with left and right hippocampal volume; scene memory correlated with right and object memory with both left and right ErC thickness. A scene-minus-object difference score correlated with Aß42 levels indicating that decreasing levels of Aß42 were associated with selective decline of scene discrimination. When considering only healthy older adults, object discrimination relatively selectively correlated with right and left hippocampal volume (N=57), left entorhinal thickness and with phospho-tau levels (N=19). These data suggest that complex object-in-scene recognition captures variance caused by both tau and amyloid pathology. A domain-specific breakdown, however, indicates that tau-related variance tends to be captured by object discrimination whereas amyloid pathology is captured by scene discrimination performance. The findings are compatible with the possibility that object and scene discrimination track different stages of disease progression in AD.

Disclosures: D. Berron: None. **H. Schuetze:** None. **A. Cardenas-Blanco:** None. **K. Fliessbach:** None. **M. Wagner:** None. **A. Spottke:** None. **M. Reuter:** None. **S. Teipel:** None. **K. Bürger:** None. **A. Schneider:** None. **O.H. Peters:** None. **P. Nestor:** None. **J. Priller:** None. **J. Wiltfang:** None. **C. Laske:** None. **F. Jessen:** None. **E. Düzel:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.03/SS62

Topic: H.02. Human Cognition and Behavior

Support: NIH/NIA Grant AG038893

NIH/NIA Grant AG041633

Title: Atrophy of specific hippocampal subfields in mild cognitive impairment is associated with impaired verbal and visual-spatial memory

Authors: *D. SODUMS[1], C. WORKMAN[2], J. JOO[2], N. NASSERY[2], G. S. SMITH[2]
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Abstract: Hippocampal atrophy, measured with magnetic resonance imaging (MRI) is a strong predictor of cognitive decline and progression to Alzheimer's dementia (AD). Atrophy within

specific hippocampal subfields may be more sensitive to memory impairment in individuals who may be vulnerable to developing AD. MRI volumes of the whole hippocampus and hippocampal subfields were measured in individuals with mild cognitive impairment (MCI) and healthy controls and were correlated with cognitive measures. Reduced hippocampal volumes, particularly in cornu ammonis (CA) area 1, CA4, and subiculum were hypothesized to be observed in MCI compared to controls and correlated with memory impairment in the MCIs. Forty-three individuals diagnosed with MCI (19 women, mean age = 68.77± 3.07), and 35 healthy, cognitively normal, controls (14 women, mean age = 66.37 ± 7.22) underwent multi-domain neuropsychological testing and MRI (Phillips 3.0T Achieva). Hippocampal and subfield volumes were measured using the Multiple Automatically Generated Templates (MAGeT) algorithm (Pipitone et al., 2014). Between group comparisons in whole hippocampal and hippocampal subfield volumes were analyzed with linear models, using total intracranial volume as a covariate of for normalization. Partial correlations evaluated the association between whole hippocampal and subfield volumes with measures of global cognition (modified mini-mental State Examination), and verbal and visual spatial memory (California Verbal Learning Test, Brief Visuospatial Memory Test-Revised, Rey-Osterrieth complex figure test). MCIs performed significantly worse than controls in global cognition and memory ($p < 0.05$). Relative to the controls, MCIs had significantly reduced volumes, bilaterally, in the whole hippocampus, subiculum and strata radiatum/lacunosum/moleculare (SR/SL/SM) and left CA4 and left dentate gyrus ($p < 0.05$). Positive correlations between whole hippocampal volume and both verbal and visual-spatial memory were observed ($p < 0.05$). Further, SR/SL/SM, subiculum, left CA4, and left dentate gyrus subfield volumes showed positive correlations between verbal and visuospatial memory, as well as global cognition ($p < 0.05$). In conclusion, this study provides further evidence for hippocampal subfield atrophy and associations with greater memory impairment in MCI. Analysis of hippocampal subfields, combined with measures of verbal and visual-spatial memory, rather than in isolation, may have more diagnostic and prognostic significance in the pre-clinical stages of AD.

Disclosures: D. Sodums: None. **C. Workman:** None. **J. Joo:** None. **N. Nassery:** None. **G.S. Smith:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.04/SS63

Topic: H.02. Human Cognition and Behavior

Support: BB/H008217/1

Title: Patterns of hippocampal long axis dynamics change across the lifespan

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Abstract: In human neuroimaging studies, the anterior hippocampus (aHPC) was found to code for global, gist-like properties of narratives and memories, while the posterior hippocampus (pHPC) was found to code for details. In rodents, the ventral hippocampus (aHPC homologue) was found to have larger place fields and more spatially correlated firing patterns than the dorsal hippocampus (pHPC homologue), coding for larger regions of space. An open question is how neural dynamics measurable by fMRI might support this gradient of representational granularity along the anteroposterior axis. Further, it is unclear how such dynamics might change over the lifespan. We addressed these questions in the present study by developing two methods to examine the granularity of spatiotemporal representations in human fMRI. We calculated 1) intervoxel similarity by correlating each voxel's timeseries to all other voxels within aHPC and pHPC, and 2) intravoxel similarity by correlating voxelwise activity within aHPC and pHPC at each timepoint to each subsequent timepoint. Since aHPC codes for global, gist-like properties, this should be reflected in more similar neural patterns across and within voxels in aHPC relative to pHPC. We applied these measures to resting state and movie watching data from young and older adults from the CamCAN repository. Intervoxel similarity was significantly greater in aHPC, relative to pHPC, suggesting more correlated signal structure consistent with the observation in rodents. Similarity in pHPC but not aHPC was increased in older adults, relative to younger adults, suggesting an age-related reduction in variability between pHPC voxels specifically. Intervoxel similarity was greater in rest than in movie watching across the entire hippocampus, and the magnitude of this effect did not differ with age. Intravoxel similarity was not significantly different between aHPC and pHPC, but reduced in older adults, suggesting a general reduction of temporal autocorrelation. Intravoxel similarity was greater during rest than movie watching, and differed between older and younger adults more during movie watching than rest. Together, these findings reflect lower similarity between voxels in pHPC than aHPC across the lifespan, but intervoxel dynamics within pHPC become less differentiated with age. In contrast, there is a nonspecific decrease of intravoxel similarity with age. Both measures reflect task-specific modulation. These findings reflect that age-related deficits observed in fine-grained memory for detail may result from an increase in the correlation between voxels in pHPC but lower temporal autocorrelation across the entire hippocampus.

Disclosures: I. Brunec: None. **B. Bellana:** None. **M. Barense:** None. **M. Moscovitch:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.05/SS64

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 1554871

Title: Recognition memory paradoxically shielded from semantic but not perceptual interference in natural aging: A representational-hierarchical account

Authors: *D. WILSON, K. POTTER, R. A. COWELL
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Abstract: In the standard Deese-Roediger-McDermott (DRM) paradigm, false memory for unstudied lures depends upon interference created by semantic associations between those lures and studied items. It has been hypothesized that interference impairs recognition performance for older adults more than young adults due to age-related structural changes in the medial temporal lobe (MTL). According to the representational-hierarchical framework, these structural changes compromise the conjunctive representations of items within their spatial, temporal and semantic context, which are housed within MTL. These structural changes are predicted to lead to differential effects of semantic versus perceptual interference on recognition memory performance. In a modified DRM paradigm, we presented multiple interleaved lists of semantically related or phonetically/orthographically related words. We predicted that older participants would be paradoxically shielded from semantic interference when semantic associations are rendered less obvious at study (by intermixing the lists), such that young adults extract the semantic associations, but older adults do not, owing to compromised conjunctive representations. In contrast, we predicted older participants to suffer more from perceptual interference than young adults, because perceptual interference (i.e., feature-overlap between items) would be present for all participants, but older adults would lack the conjunctive representations necessary to resolve the interference. Using signal detection theory to interpret our data, we found a cross-over interaction between type of interference and age: numerically, older adults' recognition memory performance was impaired less by semantic interference than by perceptual interference and young adults' recognition memory performance was impaired less by perceptual interference than by semantic interference. We suggest that inconsistencies in the previous literature on false memory in older adults may have stemmed from using false alarm rates as the dependent variable, rather than d- prime (which provides a measure of accuracy uncontaminated by response bias). Moreover, these findings support a representational-hierarchical account of memory in which aging compromises conjunctive MTL representations.

Disclosures: D. Wilson: None. **K. Potter:** None. **R.A. Cowell:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.06/SS65

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R15AG052903

Title: Configuration of stimuli modifies the age-related associative memory deficit

Authors: *J. M. SALERNO[1], K. E. MCGRAW[1], M. ROWLEY[2], A. P. GIGLIO[3], J. M. HUHN, III[4], N. A. DENNIS[4], A. A. OVERMAN[1]
[1]Psychology Dept. & Neurosci. Program, [2]Biol. Dept., [3]Psychology Dept. & Communications Dept., Elon Univ., Elon, NC; [4]Psychology Dept., The Pennsylvania State Univ., University Park, PA

Abstract: Healthy older adults experience impairments in forming associations between pieces of information (Naveh-Benjamin, 2000). The formation of these links occurs in the medial temporal lobe (MTL), including the hippocampus. During aging, the hippocampus atrophies (Raz et al., 2005), making the formation of associations increasingly difficult. Research in younger adults has suggested that different types of associations are mediated by differing neural mechanisms (Diana, Yonelinas, & Ranganath, 2012). Additional research in younger adults has shown that the extent to which associative information is unitized can reduce the demand on the binding component of associative memory and shift processing from the hippocampus to the perirhinal cortex (Haskins et al., 2008; Diana, Yonelinas & Ranganath, 2008; Ranganath, 2010; Staresina & Davachi, 2010). The objective of this experiment was to compare item-item and item-context memory in younger and older adults by presenting the same types of stimuli (faces and scenes) as either two items or an item and a context. This was done by manipulating the configuration of the stimuli at encoding. The study consisted of four study-test blocks. Results indicate differences in processing of item-item and item-context association between age groups. This suggests that unitization plays a different role in differing types of associations, that unitization may influence older adults to recruit the perirhinal cortex more in certain types of associations, and that the configuration of stimuli at encoding can be used to induce different types of associative processing. These findings contribute to scientific theories of associative memory and age-related cognitive decline.

Disclosures: J.M. Salerno: None. **K.E. McGraw:** None. **M. Rowley:** None. **A.P. Giglio:** None. **J.M. Huhn:** None. **N.A. Dennis:** None. **A.A. Overman:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.07/SS66

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R15AG052903

Title: Testing the negative repetition effect in older adults

Authors: *B. D. WILLIAMS[1], M. E. STOCKER[1], J. D. W. STEPHENS[2], A. A. OVERMAN[1]
[1]Psychology Dept. & Neurosci. Program, Elon Univ., Elon, NC; [2]Psychology Dept., North Carolina A&T State Univ., Greensboro, NC

Abstract: In the negative repetition effect (Peterson & Mulligan, 2012), rhyming cue-target word pairs are studied in a list organized by taxonomic category of the targets. Subsequent free recall of target words is reduced by first studying the same cue-target pairs in a disorganized list. This result is predicted by the item-specific-relational framework for memory, which posits a trade-off between processing of within-trial versus inter-trial associations. Prior research in young adults has shown that the left ventrolateral prefrontal cortex (VLPFC) is important in creating relationships between items, and that VLPFC shows differences in activity in older adults compared to younger adults during associative tasks (Addis, et al., 2014). Thus, neural differences in relational processing could cause differences in the negative repetition effect across age groups. The objective of the present study was to test whether the negative repetition effect is different in older adults than in young adults. Young and older adult participants studied rhyming word pairs on either an organized list only or with an initial disorganized list prior to the organized list. At retrieval, all participants completed a free recall and then associative recognition task. Results suggest that the negative repetition effect differs across age groups, which has implications for the study of associative memory and aging.

Disclosures: B.D. Williams: None. **M.E. Stocker:** None. **J.D.W. Stephens:** None. **A.A. Overman:** 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 Grant R15AG052903.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.08/TT1

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 5R01AG030395

Title: Effects of expectation on working memory performance in cognitive aging

Authors: *V. JOHNSON, T. ZANTO, N. PADGAONKAR, A. GAZZALEY
Univ. of California, San Francisco, San Francisco, CA

Abstract: Previous research has suggested a decline in the effectiveness of older adults to benefit from cued information that guides optimal task performance. However, it is unclear what neural mechanisms may contribute to this age-related decline in expectation ability. To address this, we investigated the electrophysiological correlates of stimulus-category expectation on working memory performance in aging. Healthy younger and older adults performed a delayed recognition task where the stimulus category information was either validly cued or neutrally cued. During the task, electroencephalography (EEG) data was recorded. Behavioral results show that working memory performance in younger adults is enhanced by the predictive cue but older adults do not exhibit any cue-based benefit. Similarly, neural data shows greater alpha modulation (cued > neutral) in younger adults, compared to older adults, prior to the stimulus encoding period. These results are consistent with previous findings indicating older adults do not benefit from predictive cues and extends previous research to suggest anticipatory alpha modulation may contribute to a working memory deficit in cognitive aging.
Keywords: Attention, Aging, Memory, Anticipation

Disclosures: **V. Johnson:** None. **T. Zanto:** None. **N. Padgaonkar:** None. **A. Gazzaley:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

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Topic: H.02. Human Cognition and Behavior

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Leon Fredericq Foundation

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Inter-University Attraction Pole P7/11

Title: Impact of semantic relatedness and frequency of the association on the age-related associative deficit

Authors: *E. DELHAYE[1], C. BASTIN[2]
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Abstract: Aging is accompanied by a decline in episodic memory that partly stems from a difficulty to encode and retrieve associations between pieces of information (Naveh-Benjamin,

2000). However, this associative memory decline could be attenuated when the associations could be anchored within prior knowledge, that is, for instance, when the associations are semantically related. This would allow recognition to be based on associative familiarity, preserved in aging, as opposed to recollection that is necessary to retrieve arbitrary associations but that is impaired in aging. Thematic relationship within an association was shown to enhance the contribution of familiarity to recognition to a greater extent than categorical relationship. In this study, we tested the influence of categorical vs. thematic relationships on older adults' associative recognition, as well as the influence of the frequency of the association in order to evaluate the impact of absolute pre-experimental familiarity on associative recognition. 28 young and 29 older adults took part in the experiment. Participants first studied high and low frequency word pairs that were either related by a categorical relationship or by a thematic relationship, or unrelated. They subsequently had to discriminate between intact, recombined and new pairs during a recognition phase. A group x type of relationship ANOVA on discrimination scores showed better performance in young than in older adults, as well as better performance for thematic word pairs than for categorical and unrelated ones, with categorical word pairs being more successfully recognized than unrelated ones. However, there was no group x type of relationship interaction. In a separate analysis incorporating frequency as a variable, there was no main effect of frequency, but the three-way group x type of relationship x frequency interaction was marginal ($p=0.065$). Exploratory post-hocs revealed that there was no difference in performance between young and older adults across all "related" conditions except for categorical relationship with low-frequency of association, where older adults displayed a significantly decreased performance. The main effect of group thus seems to have been driven by the associative deficit to unrelated word pairs on the one hand, and the low performance to categorical low-frequency pairs on the other hand. Altogether, this study suggests that semantic relatedness attenuates older adults' associative deficit in most cases, except one which could probably be explained by the lack of control of the frequency of the pairs after recombination. Future studies should address this limitation.

Disclosures: E. Delhaye: None. **C. Bastin:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

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Program#/Poster#: 086.10/TT3

Topic: H.02. Human Cognition and Behavior

Support: National Medical Research Council Singapore STaR/0015/2013

Title: Sleep restriction impairs knowledge formation in adolescents

Authors: *J. N. COUSINS, K. WONG, M. W. L. CHEE
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Abstract: Many adolescents accumulate sleep loss across the school week, but it remains unclear how this sleep debt impacts on the formation of schematic knowledge, a process that underpins classroom learning. We restricted 15-18 years olds (n=29) to 5-h time-in-bed for 4 consecutive nights, prior to learning detailed facts about different species of arthropods. Learning took place across a 6-h daytime period that included frequent breaks. Retention was tested with two-alternative forced-choice questions rated for confidence (Certain, Somewhat Certain, Guess) at 30-mins, 3-days and 42-days after learning and contrasted with a control group (n=30) who had 9-h sleep opportunity every night of the study. Certain memory was significantly impaired in the sleep restricted group relative to controls at all three testing sessions ($p<0.01$). Psychomotor vigilance was also impaired after 4 nights of sleep restriction ($p<0.05$), but did not correlate significantly with memory in either group ($p>0.06$). These findings point to deficiencies in the acquisition and long-term retention of knowledge when adolescents fail to obtain the recommended daily amount of sleep, and highlights the importance of keeping good sleep habits in order to optimise learning.

Disclosures: J.N. Cousins: None. **K. Wong:** None. **M.W.L. Chee:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 086.11/TT4

Topic: H.02. Human Cognition and Behavior

Title: Neural and behavioral correlates of negative overgeneralization

Authors: *A. MATTFELD, J. W. PETTIT, A. VAZQUEZ, A. KIMBLER, C. YEGUEZ, D. L. MCMAKIN
Psychology, Florida Intl. Univ., Miami, FL

Abstract: Negative overgeneralization—the failure to discriminate among two similar but different stimuli (e.g. house fire versus campfire)—is a biomarker of anxiety that may be exacerbated around the onset of puberty. While generalization allows organisms to use past experience to guide future behavior, when maladaptive it likely contributes to the etiology of anxiety. No studies have examined the neural correlates during this sensitive period of development. We propose a test of negative overgeneralization in anxious youth at the onset of puberty. Sixteen youth between the ages of 8 and 16 years across a range of anxiety symptoms performed an emotional learning task while in the scanner followed by a surprise memory test (also in the scanner) 12-hours later. In the brain negative overgeneralization was characterized by

differences in activations in the amygdala, dentate gyrus/CA3, and CA1 subfields of the hippocampus. Behaviorally, participants were worse at correctly rejecting negative lures when compared to neutral lures ($t = 4.6$, $p = 0.0005$). To disambiguate whether the decreased tendency to correctly reject similar lures was a result of overgeneralization or a failure to discriminate we calculated a lure generalization index (LGI) operationalized as p('Old|Lure) - p('Old'|Foil) and a lure discrimination index (LDI): p('New'|Lure) - p('New'|Target). We observed a greater LGI for negative stimuli relative to neutral stimuli ($t = 3.3$, $p = 0.005$), whereas negative and neutral stimuli did not exhibit differential discriminability ($t = 0.83$, $p = 0.42$). Interestingly, the degree of negative generalization as measured by LGI was positively correlated with anxiety symptoms in our sample where participants with more anxiety symptoms generalized negative stimuli more ($r = 0.5$, $p < 0.05$). These results provide a mechanistic account for negative overgeneralization in pre-adolescent youth with anxiety.

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Poster

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Program#/Poster#: 086.12/TT5

Topic: H.02. Human Cognition and Behavior

Support: NICDH Grant HD055352

Title: Relational memory is positively associated with academic achievement among preadolescent children

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Abstract: Standardized assessments of academic achievement are being used with increasing frequency and from an increasingly young age to determine the educational trajectories of school-aged children and more broadly to quantify the efficacy of educational programs. Understanding the cognitive abilities that underlie academic achievement is therefore of interest to educators and policymakers alike. Cognitive functions supported by the hippocampus and its functional network interactions, including relational memory and "flexible cognition" (Rubin *et al.*, 2014) and the implementation of effective learning strategies (Voss *et al.*, 2011), are purported to be vital to academic success. Yet there is little evidence tying performance on standardized measures of academic achievement to performance on tasks assessing hippocampal function. The current study tested the association between relational memory performance and

academic achievement during preadolescence. Participants (N = 179; mean age = 8.7 years; 97 females) completed the Kaufman Test of Academic Achievement, 2nd edition (KTEA-II) along with the Mnemonic Similarity Task (MST) (Stark *et al.*, 2013) and a spatial reconstruction task designed to assess both relational memory and the resolution of memory for highly similar studied objects. A subset of participants (n=40) completed an additional spatial reconstruction relational memory task. While performance on the MST and object memory resolution were not significantly associated with academic achievement, relational memory performance was positively associated with mathematics, written language, and overall academic achievement. The association between relational memory and academic achievement remained significant even after controlling for demographic factors including age, sex, and socioeconomic status. These findings suggest that the processes that underlie relational memory performance can be critical for academic success.

Disclosures: K.M. Hassevoort: None. **C.H. Hillman:** None. **N.A. Khan:** None. **N.J. Cohen:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

Location: Halls A-C

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Program#/Poster#: 086.13/TT6

Topic: H.02. Human Cognition and Behavior

Support: MRC Grant G030011765439

MRC Grant G100227698624

Title: Context reinstatement in developmental amnesia

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Abstract: Recollection involves bringing back to mind a prior event, including the sights and sounds associated with that experience. Patients with developmental amnesia (DA) have hippocampal damage and show a deficit in recollection such that they are not able to recall unique experiences, yet are able to generalise across multiple similar events. It is possible that some contextual information is retrieved in DA at a level which is insufficient to support recall, but sufficient for a decontextualized representation of the event. To test this hypothesis, we investigated context reinstatement in 4 patients with DA and 20 controls. On each encoding trial, a word was overlaid on an image and presented on the left, centre, or right side of the visual

field. The background images were rural, urban and scrambled scenes. Two memory tasks were conducted during fMRI. In the Background task, participants were instructed to remember the image that accompanied each word, whereas in the Location task, they had to remember the location in which each word was presented. Behaviourally, all controls performed above chance, whereas patients performed at chance levels. fMRI data in the controls showed the typical pattern of scene reinstatement, such that words that were previously paired with scenes were associated with greater activity in the parahippocampal and retrosplenial cortices than words paired with scrambled scenes. Interestingly, patients also showed scene reinstatement effects, but these were localised in the visual cortex, and not the regions that are typically associated with scene memory. For both groups, scene reinstatement effects were present in the Background Task, but not in the Location Task, suggesting that reinstatement is dependent on the retrieval goal. A functional localiser indicated that scene processing engaged the same regions in both groups. These data indicate that patients are able to reinstate aspects of their prior experience (i.e. visual context) in a strategically-directed way, but that this reinstatement is qualitatively different from that of controls and is insufficient to support context-dependent memory responses. We conclude that limited sub-threshold context memory processes occur in DA, despite the profound impairment in recollection.

Disclosures: R. Elward: None. **M.D. Rugg:** None. **M. Mishkin:** None. **F. Vargha-Khadem:** None.

Poster

086. Human Long-Term Memory in Children and in the Elderly

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Topic: H.02. Human Cognition and Behavior

Support: MRC Grant G030011765439

MRC Grant G100227698624

Title: Reduced hippocampal volumes and novelty preference in infants with corrected cardiac defects

Authors: *M. MARTINOU[1], R. ELWARD[2], M. K. SAINI[3], D. GADIAN[4], M. DE HAAN[5], M. MISHKIN[6], D. CARMICHAEL[4], T. BALDEWEG[5], F. VARGHA-KHADEM[5]
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Abstract: Neonates with TGA suffer significant cyanosis at birth and are at risk of hypoxic/ischaemic (HI) events prior to, and during their corrective surgery. Previous studies have shown that the immature hippocampus is vulnerable to HI injury, but there are no prospective studies examining the effects of HI on hippocampal structure and function in infants with TGA. We recruited a group of neonates with corrective surgery for TGA, and a group of healthy controls. All infants underwent MRI scanning between 6-12 weeks of age. Subsequently, between 24-48 weeks, their cognition, language and motor trajectories were assessed with the standardised Bayley Scales of Infant and Toddler Development, and their novelty-preference tested with a visual paired-comparison (VPC) task, where they habituated to a visual image on the screen. Infants were then shown the 'habituated to' image alongside a novel one for 5 seconds on each side. There was no delay between habituation and test. The proportion of time attending to the novel image served as the measure of novelty detection. The hippocampus was measured manually blind to group membership using MRIcron. A second rater measured 20% of the scans and an intraclass correlation coefficient (ICC) was calculated. Results of 13 infants with TGA (mean age: 30.4 weeks) were compared to those of 18 controls (mean age: 45 weeks). Inter-rater reliability was high with an ICC of 0.91 ($p=0.004$). Age-corrected mean hippocampal volumes were significantly smaller in the TGA compared to the control group ($M=1278$ mm^3 vs $M=1481$ mm^3; $F=22.26$, $p<0.001$). Fourteen participants provided data on the VPC task (7 TGA). Whereas controls showed a significant novelty preference ($M=0.66$; $t=5.94$, $p=0.001$), patients with TGA did not ($M=0.59$; $t=1.29$, $p=0.24$). Larger mean hippocampal volumes were associated with stronger novelty preference across all participants ($r=0.58$, $p=0.031$), although this association was particularly strong in the TGA group ($r=0.86$, $p=0.014$). These results suggest that the hippocampus seems to contribute to novelty detection from an early age. Furthermore, they provide new information about the early events that lead to reduced hippocampal volume and memory impairment in middle childhood in patients with TGA (Munoz et al., 2017).

Disclosures: **M. Martinou:** None. **R. Elward:** None. **M.K. Saini:** None. **D. Gadian:** None. **M. De Haan:** None. **M. Mishkin:** None. **D. Carmichael:** None. **T. Baldeweg:** None. **F. Vargha-Khadem:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.01/TT8

Topic: H.02. Human Cognition and Behavior

Support: Spanish MINECO Grant PSI2012-31448

Title: The neural basis of sign language processing: Evidence from hearing bimodal bilinguals

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Abstract: Sign language (SL) provides the opportunity to examine modality effects in language processing. Previous neuroimaging evidence has shown that SL recruits a similar set of left-lateralized perisylvian regions to those engaged in spoken languages, including the inferior frontal gyrus (IFG). However, there are still many unanswered questions regarding the functional dynamics supporting SL processing: Does regional engagement of left-lateralized perisylvian regions during language processing differ as a function of modality? Is there a specific functional signature of SL processing? To what extent does language processing rely on different neural dynamics as a function of being a native versus a L2 signer?
The present fMRI study sought to investigate these questions in several groups of hearing bilinguals: 23 native Spanish Sign Language (LSE)-Spanish bilinguals, 20 late LSE-Spanish bilinguals and 23 bilingual controls without LSE knowledge. During scanning participants processed LSE signs, presented as (silent) videos, and Spanish words, presented either aurally (sound only) or audiovisually (a video of a model saying the word with sound). Each of these three types of stimuli was contrasted to corresponding baselines, consisting of scrambled video and/or rotated speech.
Results confirmed that SL and spoken language recruited a similar set of left-perisylvian regions. Nevertheless, signers exhibited significant stronger regional engagement for SL processing than for spoken language processing across left-perisylvian nodes (Fig. 1A). Moreover, signers showed stronger activation in left IFG to process signs compared to sign-naïve controls (Fig. 1B). Furthermore, L2 signers showed involvement of the right parietal lobe relative to native signers (Fig. 1C). These results constitute the strongest evidence so far showing differential modality-specific neural dynamics involving SL processing in hearing bilinguals.

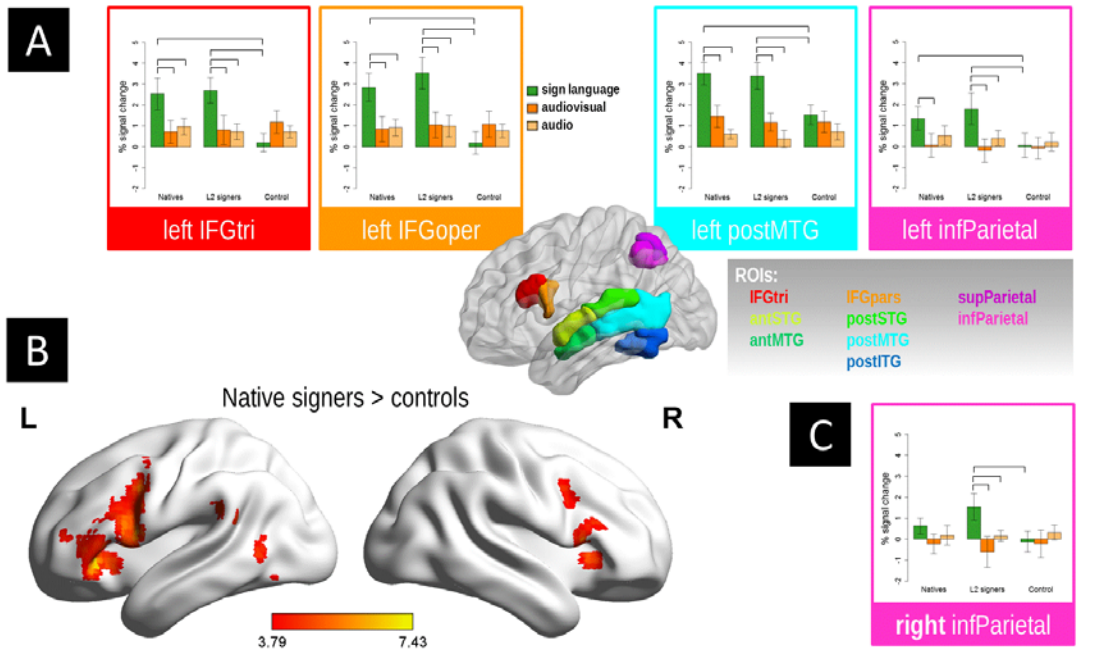

Figure 1
A. ROI analysis in language areas of the left hemisphere, showing greater recruitment for sign language processing compared to spoken language processing.
B. Whole-brain comparison between native signers and controls for the contrast signs versus baseline (FDR q<0.01, k>20).
C. ROI analysis for the right inferior parietal lobe, revealing a divergence between native and non-native signers.

Disclosures: **B. Costello:** None. **P. Paz-Alonso:** None. **M. Carreiras:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.02/TT9

Topic: H.02. Human Cognition and Behavior

Support: NSF

Title: Prepared to read. Mind wandering during oral reading correlated with resting state fMRI: A lagged analysis

Authors: ***E. E. JAHNER**[1], X. F. YANG[2], M. IMMORDINO-YANG[2]
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Abstract: What did I just read? This question is familiar to all of us. While continuing to read, we may attend to thoughts divergent from the content of the text. This can happen when reading

becomes automated; automated tasks increase the frequency of off-task thoughts. This is problematic because while attending to simple tasks that require little attention, reading without attending to content will not lead to comprehension. When we notice our attention drifting, reading aloud is one popular way to reassert this attention. Also, the use of prosodic markers may support meaning and give structure to the text. Reading aloud also gives educators a way of evaluating fluency. However, reading aloud does not always decrease mind wandering and may in fact increase its frequency. Here, we explore what might be individual behavioral and neurological differences that contribute to mind wandering frequency during oral reading. Literacy itself restructures our brains and leaves a neurological representation of the gained skill. It is not a far leap to assume that literacy practices would lead to similar persistent restructuring. One place to look for these persistent representational differences is in the dynamic systems of cortical activity of the resting brain potentially revealing neural readiness for skillful engagement with the world which includes reading aloud. This exploratory study examines resting state network activity over time and how it correlates with the frequency of mind wandering while reading aloud. We will explore how identified differences might contribute to the frequency of mind wandering while reading aloud.

Disclosures: E.E. Jahner: None. **X.F. Yang:** None. **M. Immordino-Yang:** None.

Poster

087. Understanding and Producing Language in Health and Disease

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Topic: H.02. Human Cognition and Behavior

Support: NSF BCS1026934

Title: EEG MVPA provides evidence for short latency semantic representations in temporal and parietal areas compatible with a feedforward simple-to-complex hierarchy

Authors: *S. R. DAMERA, P. S. MALONE, C. SCHOLL, J. S. KIM, M. RIESENHUBER
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Abstract: The neural substrates of semantic representation have been the subject of much controversy. Recent studies have provided support for the existence of semantic representations in the anterior temporal lobe (ATL), as a continuation of the “simple-to-complex” ventral stream object recognition processing hierarchy, with shape-based representations in ventral temporal cortex providing input to semantic representations in ATL. This model would predict latencies of semantic representations located in the ATL of less than 200ms, based on reports of high-level shape representations in ventral temporal cortex with latencies of less than 170ms (the N170). Yet, incompatible with this simple feedforward model of semantic processing, the most common

temporal marker of semantic processing, the N400, at its earliest is thought to start at ~250ms post-stimulus, over centro-parietal channels. We here trained human subjects to associate pseudowords (TPWs) with various animal and tool categories, following the design of our previous fMRI study (Malone et al., J Neurosci, 2016). This experimental design permitted us to selectively probe semantic presentations unconfounded by perceptual similarities. To decode the latency and location of semantic representations of these TPWs, we used multivariate pattern classification of EEG data acquired while subjects performed a semantic classification task. Crucially, the classifiers were trained and tested on disjoint sets of TPWs, so that the classifier had to use the semantic information from the training set to correctly classify the test set. Animal and tool TPWs were successfully classified based on EEG activity as early as 180ms. Estimated sources of this selective activation were localized to the left ATL. In addition, tools (but not animals) were successfully decoded from posterior channels by that time as well, compatible with putative sources in parietal cortex. Finally, a cluster of electrodes corresponding with the N170, a marker of visual word form processing, was identified. This was used as a seed in a whole brain coherence analysis to probe how information flowed from orthographic to semantic representations. This preliminary analysis indicated increased coherence between the N170 cluster and electrodes that showed significant animal versus tool classification. Together, our results provide evidence for access to semantic representations in the ventral visual stream that occur faster than previously reported, compatible with a feedforward account from shape-to-semantic representations

Disclosures: S.R. Damera: None. **P.S. Malone:** None. **C. Scholl:** None. **J.S. Kim:** None. **M. Riesenhuber:** None.

Poster

087. Understanding and Producing Language in Health and Disease

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Program#/Poster#: 087.04/TT11

Topic: H.02. Human Cognition and Behavior

Support: Mabel H. Flory Foundation

NIH Grant R00-HD065839

Title: Brain bases of acquired reading impairments in stroke

Authors: *W. W. GRAVES[1], O. BOUKRINA[2], A. BARRETT[3]
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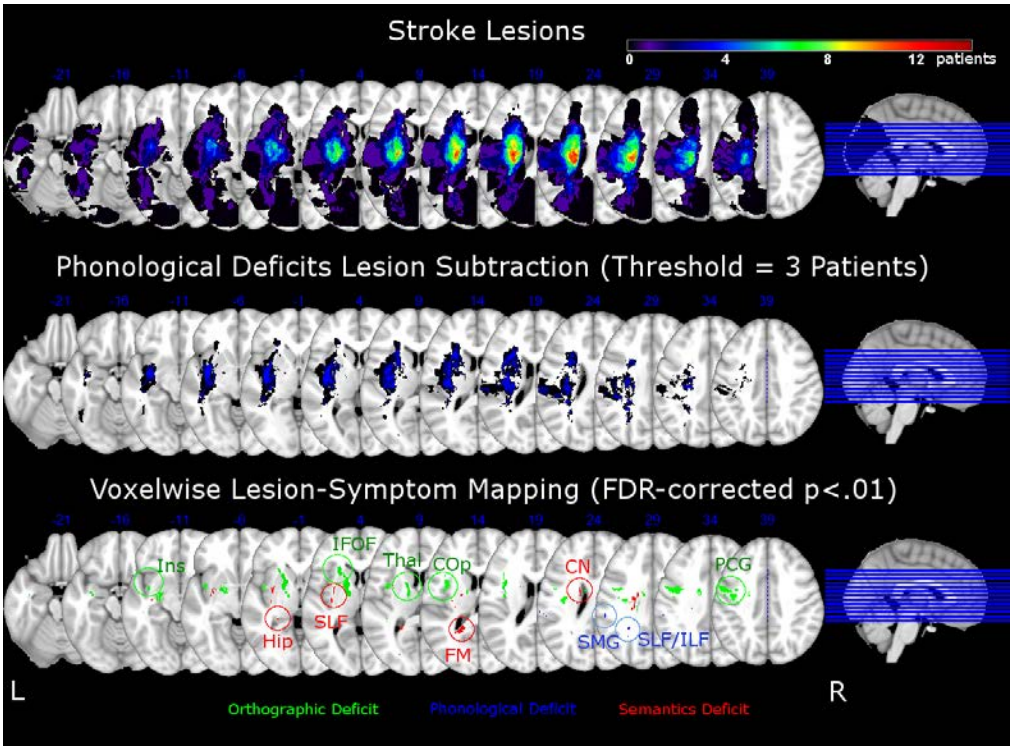
Abstract: The ability to read is an essential part of today's society and its disruption, for example, as a result of stroke, represents a significant handicap. While much work has been devoted to studying the cognitive components of typical reading and their neuroimaging correlates, little is known about the brain lesion - reading deficit associations after stroke. In this study, we sought to identify what brain areas are necessary for supporting the cognitive components of reading: orthography (visual word form), phonology (auditory word form) and semantics (word meaning), by examining the patterns of reading deficits in a cohort of left stroke survivors. We studied 23 patients (Age = 62 y., SD = 11 y.; 13 females) undergoing rehabilitation. All but one were within the first 5 weeks post-stroke, a period likely to reveal reading deficits. Patients completed computerized touch-screen tests of semantics, phonology, and orthography. In the semantic task, patients matched one of two words (or pictures) to a target based on meaning similarity. In the phonology task, the match among pseudoword stimuli was based on rhyming. In the orthography task, patients selected the most word-like string, where strings either matched or mismatched English orthographic properties. We used a subtraction analysis to identify lesion locations in patients who performed below chance on these tasks as compared to patients scoring above chance. This analysis revealed lesions in supramarginal gyrus, Heschl's gyrus, and the SLF, associated with phonological deficits. A voxel-based lesion-symptom mapping analysis, considering continuous scores along all 3 reading components, supported this result, and additionally revealed correlates of orthographic function in the precentral gyrus, insula, thalamus, and the inferior fronto-occipital fasciculus; and semantic function in the hippocampus, caudate, and adjacent white matter (Fig. 1). Our results support the notion that the same neural structures underlie phonology in speech and print, and implicate frontal and subcortical regions in orthographic processing.



Disclosures: **W.W. Graves:** None. **O. Boukrina:** None. **A. Barrett:** None.

Poster

087. Understanding and Producing Language in Health and Disease

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Program#/Poster#: 087.05/TT12

Topic: H.02. Human Cognition and Behavior

Support: DC015260

Title: Neuronal activity in the human subthalamic nucleus during speech production

Authors: *A. RAMÍREZ-CÁRDENAS[1], K. TJADEN[2], L. KOPF[3], H. CHEN[1], K. BRYANT[3], D. CORCOS[4], J. D. GREENLEE[1]
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Abstract: Like other motor behaviors, speech requires the sequencing and control of simpler movements into a coordinated action. Accordingly, the basal ganglia are thought to play an important role in speech programming, initiation, execution, and control. Moreover, recent evidence suggests that basal ganglia involvement extends beyond the strict motor aspects of speech, to a role in language and decision making. This is particularly the case for the subthalamic nucleus (STN). In the present study, we want to investigate whether neural activity in the subthalamic nucleus is modulated by speech complexity. For that purpose, we recorded LFPs and spiking activity in the subthalamic nucleus of four patients who underwent deep brain stimulation (DBS) surgery for clinical reasons. Data were collected while subjects produced utterances with different levels of complexity (sustained vowels, word repetition, sentence repetition and free monologue). Subject utterances were captured with a microphone for further examination. Preliminary analyses of the data show a modulation in beta power for all types of utterances. Particularly, beta power was suppressed during speech production. Our results advance our understanding on the role of the basal ganglia in language processing and production.

Disclosures: **A. Ramírez-Cárdenas:** None. **K. Tjaden:** None. **L. Kopf:** None. **H. Chen:** None. **K. Bryant:** None. **D. Corcos:** None. **J.D. Greenlee:** None.

Poster

087. Understanding and Producing Language in Health and Disease

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Topic: H.02. Human Cognition and Behavior

Support: NICHD Grant HD079779

C. V. Starr Postdoctoral Fellowship

Title: The importance of "motherese": Early drivers of successful communication

Authors: *E. A. PIAZZA, M. C. IORDAN, U. HASSON, C. LEW-WILLIAMS
Princeton Univ., Princeton, NJ

Abstract: The voice is the most direct link we have to others' minds, allowing us to communicate using a rich variety of cues. This link is particularly critical early in life, as parents draw infants into the structure of their environment using infant-directed speech (IDS), a communicative code with unique pitch and rhythmic characteristics relative to adult-directed speech (ADS) (Fernald, 1992). To begin breaking into language, infants must discern subtle statistical differences about people and voices in order to direct their attention toward the most relevant signals.

Here, we first reveal a new defining feature of IDS: mothers significantly alter statistical properties of their vocal timbre when speaking to their infants. Timbre, or tone color, is a spectral fingerprint that helps us instantly identify and classify sound sources, such as individual people and musical instruments. We recorded 24 mothers' naturalistic speech while they interacted with their infants and with adult experimenters in their native language. Half of the participants were English speakers, and half were not. Using an SVM classifier, we found that mothers consistently shifted their timbre between ADS and IDS. Importantly, this shift was highly similar across languages (i.e., a classifier trained to discriminate IDS from ADS on English data alone could distinguish the two modes when tested on non-English data, and vice versa), suggesting that such alterations of timbre are universal. Furthermore, this shift could not be explained by differences in pitch or background noise across conditions. These findings have theoretical implications for understanding how infants tune in to their local communicative environments and could inform educational tools aimed at enhancing children's learning.

In ongoing work, we are using fNIRS to investigate neural coupling between caregivers and their infants. Previous research using fMRI (Stephens et al., 2010) and fNIRS (Liu et al., 2017) has shown that neural synchrony, between a speaker and listeners, underlies successful communication during storytelling. One prediction of our multifaceted developmental project is that the prosodic cues contained in IDS are instrumental in harnessing effective caregiver-child neural coupling during naturalistic interactions, which translates into better language learning.

This work could have broad implications for the origins of human communication and may eventually provide early biomarkers for disorders such as autism.

Disclosures: E.A. Piazza: None. **M.C. Iordan:** None. **U. Hasson:** None. **C. Lew-Williams:** None.

Poster

087. Understanding and Producing Language in Health and Disease

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R00 HD065839

Title: Multivariate pattern analysis reveals semantic information in brain areas activated for nonwords

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Abstract: The neural basis of semantic cognition has been investigated using univariate analysis of functional magnetic resonance imaging (fMRI) data for at least the past 20 years. These analyses have proven to be very effective in revealing neural regions involved in the putative neural semantic network, which significantly overlaps with the default mode network (DMN). However, there have been some inconsistencies across fMRI studies in terms of the primary regions involved in semantic processing. These discrepancies have most often been found in studies that manipulate the level of task difficulty, where increasing levels of difficulty activate regions outside of the putative semantic network/DMN, such as the task positive network (TPN). We recently observed this pattern in a lexical decision task with high and low imageability words, where the word-nonword contrast revealed nonword activation primarily in the DMN (including angular gyrus and posterior cingulate), and word activation in the TPN (including inferior frontal junction, intraparietal sulcus, and ventral occipitotemporal sulcus). Here we investigated whether the putative semantic areas activated for nonwords also encoded semantic information. This was determined by classifying high and low imageability words using multivariate pattern analysis (MVPA), implemented in the PyMVPA suite. We trained a Sparse Multinomial Logistic Regression classifier on fMRI data restricted to the nonword contrast to determine whether participants were reading high or low imageability words. It reliably classified imageability category at 83.3% accuracy ($p < .05$ by Monte Carlo simulation). This suggests that semantic information is present even
in areas activated by meaningless nonwords. Although previous activation of putative semantic

areas by nonwords was presumably due to difficulty effects, this analysis shows difficulty effects and semantic information can co-localize in the same neural network.

Disclosures: H.J. Levinson: None. **S. Mattheiss:** None. **W.W. Graves:** None.

Poster

087. Understanding and Producing Language in Health and Disease

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Program#/Poster#: 087.08/TT15

Topic: H.02. Human Cognition and Behavior

Support: SFI 15/CDA/3316

Title: Indexing the semantic processing of natural speech with EEG

Authors: *E. C. LALOR[1], M. P. BRODERICK[3], G. M. DI LIBERTO[4], A. ANDERSON[2]
[2]Biomed. Engin., [1]Univ. of Rochester, Rochester, NY; [3]Neural Engin., [4]Trinity Col. Dublin, Dublin, Ireland

Abstract: Studies of natural language processing using EEG have typically measured neural activation for short snippets of language, and contrasted EEG responses to subtle variations in linguistic stimuli. For instance, the well known N400 effect can be revealed by contrasting the time-aligned EEG response to sentences such as the "the dentist told me to brush my teeth" with "the dentist told me to brush my tree". Although such approaches have been the foundation of an extensive body of research, they tend to be grounded on artificial modulations of a small stimulus set that is constrained to be amenable to conventional analyses. How much the results generalize to natural language is unclear. Consequently, there has been a recent move toward EEG-based analyses of more natural linguistic stimuli. We here build on related work on natural speech (audio-book) comprehension that used time-stamped models of the acoustic and phonemic properties of speech to predict and disentangle associated EEG signal. This demonstrated that EEG signal exclusively associated with phonemic properties of speech could be extracted, thus supporting the inference that the acoustic stimulus had been first decoded into speech units by the experimentee's brain. We here go beyond this, and build a measure that enables the further inference that the experimentee also processed words' meanings. We do this by adding in an additional "semantic" layer to the acoustic and phonemic features of the earlier predictive model. We exploit the recently popular "word2vec" computational model of words' meanings as the basis for semantic prediction. By computing the semantic difference between a word and the words in the previous phrase we build a predictive measure of "semantic surprisal": if a new word's meaning is not correlated with the previous words' meanings then it is a surprise! We demonstrate that: the EEG response to high semantic surprisal words closely adheres to the conventional N400 response; that the magnitude of this effect is modulated by the

magnitude of semantic surprisal; and that this effect disappears in reversed and unattended speech. This work provides a new index of semantic comprehension in natural speech, which has implications for both cognitive and clinical neuroscience.

Disclosures: E.C. Lalor: None. **M.P. Broderick:** None. **G.M. Di Liberto:** None. **A. Anderson:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.09/TT16

Topic: H.02. Human Cognition and Behavior

Title: Intrinsic Cerebro-Cerebellar Functional Connectivity reveals the function of cerebellum VI in reading

Authors: *C. ANG[1], X. FENG[1], H. LI[1], M. ZHANG[2], X. YANG[2], M. TIAN[3], Y. GAO[1], X. MENG[2], G. DING[1]
[1]Beijing Normal Univ., Beijing, China; [2]Peking Univ., Beijing, China; [3]Inst. of psychology, Chinese Acad. of Sci., Beijing, China

Abstract: Introduction: Increasing evidences showed that the cerebellum, particularly cerebellum VI, plays an important role in reading. The engagement of cerebellum VI in language processing was found in typical developed readers (Stoodley & Stein, 2011) and in dyslexia readers (Feng et al., 2016; Stanberry et al., 2006). A recent study found cerebellum VI compensated for reading impairment through the connections with specific brain regions for different reading tasks (Feng et al., 2016). Reading difficulties may be caused by impairments of either phonological awareness(PA) or rapid naming (RAN) (Norton et al., 2014). However, it is not clear whether and how the function of cerebellum VI is related to the performance in PA and RAN. Here we used resting-state MRI to explore how the intrinsic cerebro-cerebellar functional connectivity of cerebellum VI related to PA and RAN. Our first goal was to test the hypothesis that the role of cerebellum VI in different language tasks is implemented through functional connection to different cerebral regions responsible for the tasks. Our second goal was to compare whether function of the left and right cerebellum VI with an examination of their relevant cerebro-cerebellar functional connectivity associating different tasks. Method: Resting-state MRI data and PA/RAN scores were collected from fifty-seven typically developing readers. Left and right cerebellum VI were chosen as ROIs from a meta-analysis study (E, Chen, Ho, & Desmond, 2014), and then the correlations between ROI-wise cerebro-cerebellar functional connectivity and reading performance were analyzed. Results: For the PA task, our results revealed a significant positive correlation between PA scores and the functional connectivity of right cerebellum VI to bilateral insula. Similar results were found in the left cerebellum VI,

where there is positive correlation between PA scores and its functional connectivity to bilateral insula and left postcentral gyrus. For the RAN task: our results revealed a significant negative correlation between RAN reaction time and the functional connectivity of the right cerebellum VI to left postcentral gyrus. Similar results were also found at the left cerebellum VI. In conclusion, the connections between bilateral insula and cerebellum VI were related to PA, and the connections between left postcentral gyrus and cerebellum VI were related to RAN. The results verified the hypothesis that the cerebellum VI functions through the connection to different cerebral regions to carry on different language tasks, and the function of the left and right cerebellum VI does not differ.

Disclosures: C. Ang: None. **X. Feng:** None. **H. Li:** None. **M. Zhang:** None. **X. Yang:** None. **M. Tian:** None. **Y. Gao:** None. **X. Meng:** None. **G. Ding:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.10/TT17

Topic: H.02. Human Cognition and Behavior

Title: Cerebro-cerebellar network plasticity in chronic left-hemisphere stroke revealed by resting state functional connectivity

Authors: *A. T. DEMARCO[1], P. TURKELTAUB[1], C. J. STOODLEY[2]
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Abstract: In recent decades the cerebellum has been recognized for its contribution to multiple aspects of higher cognition, including linguistic and spatial processing, executive function, and affect. Within the linguistic domain, the cerebellum has been implicated in a range of functions, including speech perception and planning, verbal working memory and fluency, and grammar processing. Meta-analyses of fMRI studies reporting cerebellar activation have suggested a subregion of right lobule VIIa, Crus I, is engaged during non-motor aspects of language tasks. Mapping cerebellar resting state functional connectivity (rsFC) has shown that this region is coupled to the cortical frontoparietal cognitive control network, which both overlaps and interacts with the language network and may play a role in aphasia recovery. Although alterations to cerebro-cerebellar connectivity have been documented in reports of crossed cerebellar diaschisis in aphasia, the nature and dynamics of such a network breakdown remain unclear. Here we examined this relationship as a function of lesion location by analyzing whole-brain rsFC seeded from right Crus I in a group of individuals with chronic left-hemisphere stroke (N = 46; mean age 59.6 years, range 37.6 to 77.8). First we identified left-hemisphere peaks of whole-brain rsFC with a seed placed in right Crus I in a healthy control group (N = 40; mean age

58.9, range 26.2 to 80.2). We then contrasted rsFC maps between patients who did or did not have damage at the coordinates of each peak. We found that lesion location was associated with differences in rsFC between right Crus I and right inferior frontal cortex and supplementary motor area. Specifically, lesions involving posterior perisylvian cortex in peaks centered on posterior superior temporal gyrus (MNI = -59, -30 -6; 14/46 lesioned), supramarginal gyrus (MNI = -56, -51, 22; 18/46 lesioned), and angular gyrus (MNI = -51, -61, 22; 17/46 lesioned) were associated with greater rsFC relative to lesions sparing those regions. Region of interest analyses showed that, relative to controls, rsFC was enhanced in patients with posterior lesions and diminished in patients with lesions elsewhere. These findings show that alterations to cerebro-cerebellar functional connectivity in chronic left-hemisphere stroke is sensitive to lesion location, suggesting a nuanced interplay between the cerebellum and the cortical language network.

Disclosures: A.T. Demarco: None. **P. Turkeltaub:** None. **C.J. Stoodley:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.11/TT18

Topic: H.02. Human Cognition and Behavior

Support: The Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2017R1A2B4006604)

Title: EEG-based time-frequency analysis for case marker violation task in verb-final language

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Abstract: Electroencephalography (EEG) is frequently used to investigate human cognitive characteristics mostly with event-related potentials (ERPs) analyses. In general, ERP-based EEG studies try to identify statistically significant features from grand averaged waveform. However, increasing number of recent EEG studies reported that in-depth analysis on EEG data including time-frequency analysis can allow us to gain new insights underlying cognitive symptoms. In this study, we apply time-frequency analysis on double nominative and accusative linguistic research in Korean. Unlike English, Korean is a verb final language with a canonical word order of Subject-Object-Verb. Previous study investigated that linguistic case marker violation conditions evoke noticeable patten in ERP waveforms. In this experiment, participants are seated

in sound-attenuated room. Stimuli sentences are consists of normal, and case marker violation sentences with double nominative case marker violation, and double accusative case marker violation. Sentences are visually presented phrase-by-phrase, followed by a blank screen for base fixation. For analysis, we performed time-frequency analysis with the recorded continuos EEGs and examined underlying in-depth neuronal characteristics involved with this language cognitive tasks.

Disclosures: **J. Lee:** None. **J. Lee:** None. **J. Lee:** None. **D. Yeo:** None. **S. Oh:** None. **Y. Lee:** None. **K. Kim:** None. **J. Sung:** None. **S. Jun:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.12/TT19

Topic: H.02. Human Cognition and Behavior

Support: ANII POS_NAC_2015_1_109472

Title: Elementary composition in language processing: an EEG study

Authors: *E. FLÓ, Á. CABANA, J. C. VALLE LISBOA
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Abstract: Combining words to represent a new concept is the basic combinatorial operation needed to generate and understand meaningful phrases. The elaboration of these complex structures of related concepts entail both syntactic and semantic composition processes which are difficult to disengage.
Previous research in which stimuli were restricted to simple composition using MEG and fMRI have identified the left anterior temporal lobe to be involved in conceptual combinatory operations. In this work we aim at finding a simple composition marker in EEG using an adaptation of Bemis, D. K., & Pylkkänen, L. (2011) experimental design for Spanish. Contrary to English, Spanish noun phrases are constructed such that the adjective is preceded by the noun. Given this distinction and the original design, we decided to introduce a second task in order to establish the adequate control for the composition task.
Stimuli for the three tasks were constructed randomly for each subject from a pool of 11 words denoting nouns, 11 words denoting colors, balanced for frequency and other properties, and 11 consonant strings. The composition task consisted of 100 noun-adjective and 100 consonant string-adjective combinations, followed by an image congruent or incongruent to the verbal material. In one of the control tasks subjects were presented with combinations of noun-noun and consonant string-noun stimuli, as opposed to the second control task where participants were shown combinations of color-color and consonant string-color stimuli. In both control tasks the

verbal material was followed by an image congruent to one of the presented words or incongruent to both. The purpose of these controls was to ensure that the difference in the composition task was not due to the amount of words presented in each condition.
We performed a cluster permutation analysis to determine the spatial and temporal distribution of the neural activity related to composition. We show evidence of an activity specific to the composition task in a time window consistent with the literature.

Disclosures: **E. Fló:** None. **Á. Cabana:** None. **J.C. Valle Lisboa:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.13/TT20

Topic: H.02. Human Cognition and Behavior

Title: Using Indian orthographic stimuli-evoked ERPs to evaluate language acquisition in early primary schoolchildren

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Abstract: Indian languages are learned in an order of increasing complexity, i.e., vowels, consonants, consonants+vowel signs (*matras*) and consonantal conjuncts. We hypothesized that such linguistic visual stimuli could increase the analytical resolution of ERPs in Indians.
Methods: We used an EEG cap with dry electrodes *(Enobio8; Neuroelectrics)* to record ERPs from entry-level (1st grade, <1month) school children (n=14) in rural India (Ramanujganj Block, Balrampur District, Chhattisgarh). Each of these 4 Hindi stimuli (n=100) were randomly counterbalanced with equivalent Kannada stimuli, a language they did not know. Subjects were divided into normal active (n=7) and slow active (n=7) groups by the teacher; 4 subjects had noisy data which were discarded.
Results:
1. The Late Positive Complex (LPC) was significantly delayed (*t-test;p<0.0001*) in the slow active group in all conditions. (Fig.1).
2. Visual ERPs reflected increasing complexity of the stimuli with increased LPC positivity in all normal active subjects (Fig.2). ERPs of easy stimuli elicited by vowels (e.g.,अ) and consonants (e.g.,क) could be differentiated from ERPs elicited by hard stimuli e.g., consonant+*matra* (e.g.,

चि) and consonantal conjuncts (e.g., क्ष).

3. Occipital potentials were muted in the slow active group in all conditions.

Conclusion:

This could be a simple, objective adjunct to current psychological tests used to evaluate literacy acquisition in India, where ~10% of primary school children have dyslexia and dyscalculia.

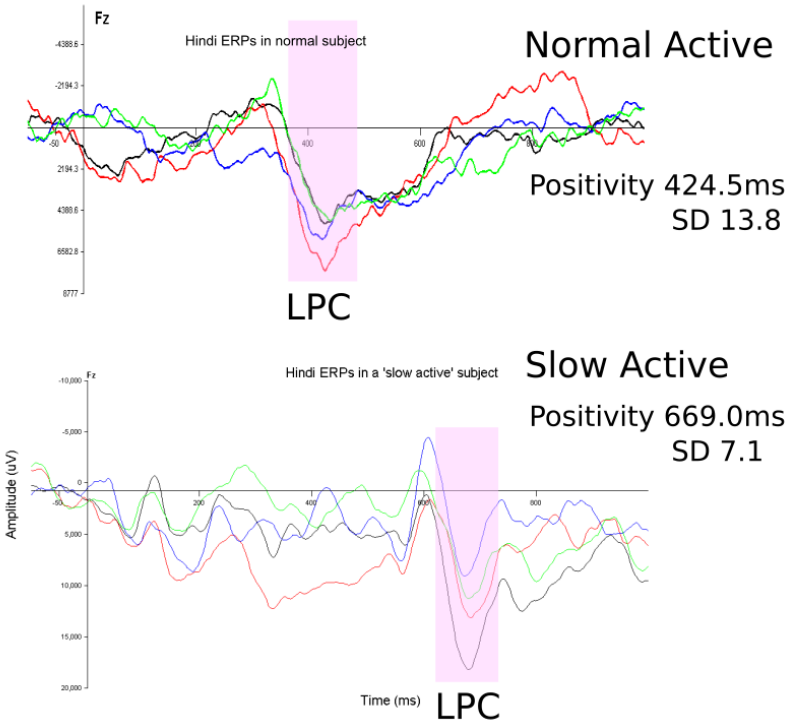

Fig.1

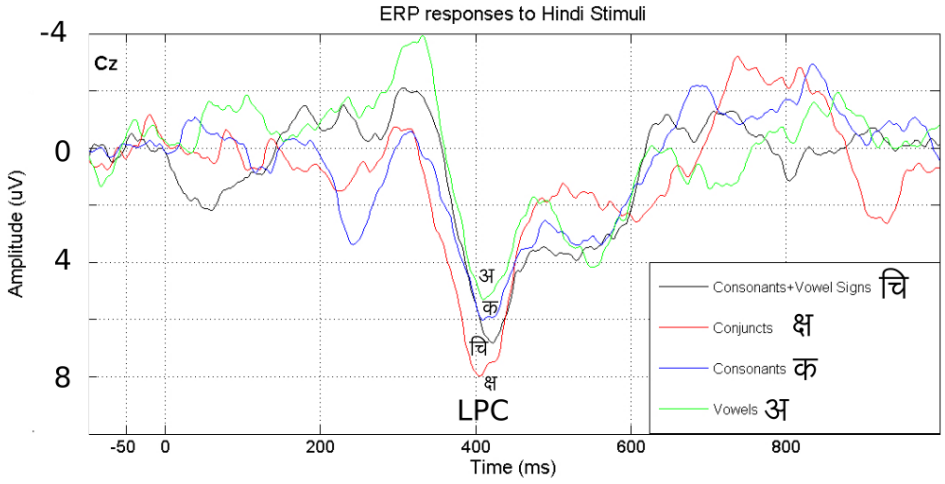

Fig.2

Disclosures: **A. Premchandra:** None. **S. Anand:** None. **A.P. Menon:** None. **K.K.V. Sankar:** None. **S. Boro:** None. **M. Jayachandra:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.14/TT21

Topic: H.02. Human Cognition and Behavior

Support: AG017586

Title: Longitudinal decline in the production of concrete nouns in svPPA

Authors: *K. A. COUSINS[1], S. ASH[3], M. GROSSMAN[2]
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Abstract: Patients with semantic variant primary progressive aphasia (svPPA) suffer a profound loss of semantic knowledge. While aphasia in svPPA is often characterized as a global semantic impairment, some studies have noted that the loss of concrete noun knowledge is more severe than for abstract nouns - a phenomenon known as 'reversal of the concreteness effect (CE)'. This concreteness impairment may be due to atrophy of the left ventral temporal lobe in svPPA; visual feature knowledge supported by the ventral temporal lobe is thought to be important for the representation of concrete nouns. However the reversal of CE is not apparent in all svPPA patients, and differences in semantic impairment may be due to differences in disease severity and the degree of atrophy of the ventral temporal lobe. This longitudinal study aims to shed light on the basis on concrete noun impairment in svPPA by examining how temporal lobe atrophy predicts the reversal of CE. To elicit a semi-structured speech samples, 12 svPPA patients were asked to describe the Cookie Theft picture (Goodglass & Kaplan, 1983) at two time points, with an average of 16.21 months between testing. Performance was compared to noun production in 32 healthy controls. For each subject, nouns produced were rated for concreteness using published norms (Brysbaert et al., 2014). We found that svPPA patients produced significantly less concrete nouns at follow-up compared to baseline and compared to controls. Next, we examined whether gray matter (GM) atrophy in svPPA at baseline predicted behavioral performance at follow-up in 6 patients with T1-weighted magnetic resonance imaging. Relative to controls, svPPA patients exhibited reduced grey matter volume to the bilateral temporal lobes. Regression analyses in svPPA restricted to regions of atrophy revealed that GM atrophy in the left fusiform gyrus and the left middle temporal gyrus at baseline predicted significantly decreased concreteness at follow-up. These results reveal the reversal of the concreteness effect in svPPA may become more severe over time, and that impaired visual feature knowledge due to atrophy of the left fusiform gyrus may contribute to this decline.

Disclosures: **K.A. Cousins:** None. **S. Ash:** None. **M. Grossman:** None.

Poster

087. Understanding and Producing Language in Health and Disease

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Program#/Poster#: 087.15/TT22

Topic: H.02. Human Cognition and Behavior

Support: BCS-1533688

DGE-1250104

Title: Analyzing functional connectivity network dynamics from ECoG data, using non-parametric graph theoretic tools in an object naming task

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Abstract: The human brain is a highly interconnected set of neuronal pathways, and the overarching goal of this project is to analyze macroscopic brain network dynamics from recordings using graph theoretical tools. Human ECoG data is obtained from cortical recordings electrodes implanted in patients undergoing epileptic surgeries who perform a multitude of language tests. The data from an articulation task is used to characterize brain dynamics using vector factor graphs in a purely data driven manner with no prior assumptions. Information theoretic connectivity metrics like mutual information (MI) are used to infer dependencies and conditional dependencies calculated with a data-driven approach using a k-nearest neighbors method for estimating entropies. Most ECoG analysis is done using high gamma band frequency, as it is associated with cognitive processing in the brain. In this work, interesting dependencies between brain regions were observed in all frequency bands, not just in the high gamma band. Mutual information in frequency is used as the connectivity metric to find the underlying graphical model in frequency. Graph theoretic algorithms are used to estimate the skeleton and equivalence class of high dimensional directed graphs using these connectivity metrics. The brain connectivity network is then inferred for each of the common frequency bands (beta, gamma and high gamma). The change in this network is evaluated with time, in each frequency band. To make holistic inferences at a macroscopic scale, vector factor graphs are used to combine network information from multiple frequency bands across time, to reveal novel patterns and shed more light on the functional connectivity patterns in the human brain during an object-naming task.

Disclosures: **S. Yellapantula:** None. **N. Tandon:** None. **B. Aazhang:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

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Program#/Poster#: 087.16/DP11/TT23 (Dynamic Poster)

Topic: H.02. Human Cognition and Behavior

Support: Neuroengineering and Medicine T32 (NS091006)

Title: Spatiotemporal activation patterns associated with self-paced verbal fluency utterances

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Abstract: BACKGROUND
Tests of verbal fluency are frequently used to evaluate linguistic and cognitive function in a variety of neurocognitive disorders including epilepsy, Alzheimer's disease and ADHD (Troyer et al. 1997). Impaired performance is considered to reflect deficits in lexical access ability and/or executive control (Shao et al. 2014). Verbal fluency tasks activate a broad network of bifrontal and bitemporal regions, most notably the left inferior frontal, precentral and fusiform gyri (Parks et al. 1988; Birn et al. 2010). However, the timing of activation of these regions has yet to be elucidated. Intracranial electroencephalography (iEEG) provides a unique opportunity to investigate the neuronal activation patterns associated with verbal fluency task performance with high spatial and temporal precision.
METHODS
We used subdural recordings to study the cortical activation patterns in 7 patients undergoing presurgical evaluation for intractable epilepsy. Silastic-embedded platinum-iridium disc electrodes (AdTech Medical) were placed over the frontal and temporal regions based on clinical necessity. Recordings were obtained at rest and during semantic and phonemic verbal fluency tasks using a Natus data acquisition system (sampling frequency 500Hz). Epochs were extracted from 1250ms prior to 750ms after onset of each utterance. High gamma (70-110Hz) spectral power was determined in 200ms moving windows with 10ms step sizes using the Thomson multitaper method (Thomson 1982), and normalized by the resting high gamma power at each electrode.
RESULTS
Four implants were predominantly left hemispheric and 3 were right-predominant. In all but one subject we observed robust increases in high gamma activity in sensorimotor cortex starting

300ms prior to utterance onset. There were also high gamma increases in posterior temporal regions starting 250ms after utterance onset. Differences between semantic and phonemic conditions varied robustly in timing and location across subjects.

DISCUSSION

To our knowledge, this is the first study using iEEG to characterize spatiotemporal activation patterns in a letter- and category-motivated free recall format. Our results are consistent with studies of stimulus-locked word generation (Edwards et al. 2010; Korzeniewska et al. 2008; Indefrey 2011). Variability in the differences between semantic and phonemic verbal fluency conditions may reflect inter-individual variability in search strategies and conceptual representations (Hirshorn & Thompson-Schill 2006; Wang et al. 2011). Further analyses will investigate the roles of lower frequency oscillatory patterns and category imageability.

Disclosures: S.T. Williams: None. **P. Shah:** None. **H. Gatens:** None. **V. Piai:** None. **A. Krieger:** None. **T.H. Lucas:** None. **B. Litt:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.17/TT24

Topic: H.02. Human Cognition and Behavior

Support: CSIC I+D 2012

CSIC RDT

ANII SNI

Title: Episodic and semantic components of lexical knowledge: a computational model

Authors: *Á. CABANA, E. FLÓ, C. ZUGARRAMURDI, J. C. VALLE-LISBOA
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Abstract: The role and structure of the lexicon have been the subject of recent debate in psycholinguistic theories. Empirical evidence shows that early semantic processing integrates semantic and pragmatic or “world knowledge” information.Some theoretical approaches account this stating that meaning is computing by integration of contextual cues from different sources, implying there may be no “meaning” of words independent of context. Other views support the interaction between a semantic lexical store and event knowledge representations to explain these effects. With the intention to test the plausibility of this dual-route approaches, here we expand a previous attempt to build a computational model with two components: a WordNet-based lexical store and a set of documents related to different types of events. We tested our model simulating the results of priming experiments in which the relationship between prime and

target either ”semantic” or “episodic” (for instance, category coordinates or nouns denoting typical participants of events). We used spreading activation functions to account priming effects: activation in the “semantic” (WordNet) module spreads to all elements of a given synset, whereas activation in the “episodic” module spreads to all words that appear in a given document. Using this approach to explore two different priming experiments, we show that there are instances in which priming can be explained mainly by activation from the semantic or the episodic modules. In most of these latter cases, clusters of event-related words are strongly represented in the “episodic” documents, whereas in the latter cases, words are represented in a wide set of unrelated documents, rendering their event-activations low. That is, when words are spread over many different types of events, the event knowledge is not relevant; in contrast, as in event nouns, event knowledge is more important.These results suggest, using a computational model, that dual-store accounts of lexical knowledge are compatible with priming patterns of event-related words.

Disclosures: **Á. Cabana:** None. **E. Fló:** None. **C. Zugarramurdi:** None. **J.C. Valle-Lisboa:** None.

Poster

087. Understanding and Producing Language in Health and Disease

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 087.18/TT25

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01-DC-014085

NIH Grant T32-DC010775

Title: Neural source dynamics of brain responses to continuous speech: From acoustics to comprehension

Authors: *C. BRODBECK[1], A. PRESACCO[3], J. Z. SIMON[2]
[1]Inst. for Systems Res., [2]Biol., Univ. of Maryland, College Park, MD; [3]Otolaryngology, Univ. of California, Irvine, Irvine, CA

Abstract: Natural speech processing is inherently difficult to study with neuroimaging methods because of the temporal and acoustic irregularity of continuous speech; much of what we know about the neural basis of language comprehension is based on experimental designs that sacrifice naturalness of the stimuli, leaving open the question of whether neural processing differs in more realistic settings. To address this issue, we combined source estimation of magnetoencephalography (MEG) data with reverse correlation to predict the neural response to different properties of continuous speech in time as well as by anatomical location. We first

computed distributed minimum norm current estimates for the MEG responses of young adults listening to segments of an audiobook, and then used reverse correlation based on the boosting algorithm to compute response functions for different predictors at each virtual current source. Response functions were statistically assessed with permutation tests. Results show neural processing of multiple levels of the speech stimulus: An early (~50 ms) response to the acoustic envelope of the speech stimulus separates into an earlier (~35 ms) response in auditory cortex, and a later (~50 ms) more dorsal response, consistent with the mouth area of somatosensory cortex, suggesting fast mapping of acoustic information to somatosensory/motor representations. A later response to the acoustic envelope (~100 ms) localized predominantly in right auditory cortex, while a response associated with word-frequency was localized to left auditory cortex, suggesting differential processing of acoustic and lexical information in the two hemispheres. Finally, a response to words that enable semantic composition is seen in higher level language areas, anterior temporal lobe and inferior frontal gyrus, demonstrating that even comprehension-related responses can be localized with reverse correlation. Our results indicate that MEG responses to continuous speech are rich in dynamic information that can be spatially reconstructed. This extends the set of possible hypotheses about the neural basis of speech comprehension that can be tested in the natural setting of listening to continuous speech.

Disclosures: C. Brodbeck: None. **A. Presacco:** None. **J.Z. Simon:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.01/TT26

Topic: H.02. Human Cognition and Behavior

Support: NSF

Title: A neurally-informed model of sensory- and motor-level biases in rapid sensorimotor decision making

Authors: *K. AFACAN[1], S. KELLY[2]
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Abstract: When we must act extremely fast in response to sensory cues, sensorimotor decisions must be biased towards higher-value options to maximize rewards. We recently reported that under such circumstances, humans show behavioral and electrophysiological patterns consistent with a temporally increasing evidence representation in addition to a value-based shift in “drift rate” of an accumulate-to-bound decision process, contrary to dominant, “starting-point bias” mechanisms that best explain deliberative, perceptual judgments. Here we report on follow-up

work in which we A) develop a neurally plausible version of this cognitive model, and B) test the contextual specificity of the bias effect. In our task, subjects performed rapid, suprathreshold color discrimination reported through left/right hand button clicks within a very strict deadline, with one alternative rewarded more points than the other if correct. In our Value-Modulated Sensory Response model, feature-tuned neural populations initially respond non-selectively, but their selectivity increases over time. The population tuned for the higher value feature is multiplicatively boosted relative to the lower-value population, predicting that on presentation of a low-value cue, differential evidence (and hence drift rate) initially favors the incorrect higher value alternative but over time switches to favoring the correct alternative, resulting in a turn-around in cumulative evidence that is reflected in electroencephalographic signatures of motor preparation. Based on further neural signal observations we endow the model with systematic value-based shifts as well as random variability in starting point, and show that its simulation replicates the main features of motor preparation waveforms. While subjects were informed about the value-color associations before the blocks in the original task, in the new version they are informed of the value-response hand associations before the blocks, where value-color mapping changed randomly from trial to trial. In this scenario, we still observe behavioral and electrophysiological signatures of sensory-level biasing. Thus, value-modulation of sensory responses may be a general mechanism that applies in any severely time-restricted sensorimotor task regardless of time-scale of value association.

Disclosures: **K. Afacan:** None. **S. Kelly:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.02/TT27

Topic: H.02. Human Cognition and Behavior

Support: CV Starr Foundation Fellowship

Title: Control mechanisms for flexibility in a changing world

Authors: ***B. A. EBITZ**[1], J. D. COHEN[2], T. BUSCHMAN[2]
[2]Princeton Neurosci. Inst. & Dept of Psychology, [1]Princeton Univ., Princeton, NJ

Abstract: The world is never stable for long. Therefore, we have evolved the capacity to flexibly adjust our behavior when the environment changes. Yet, much remains to be learned about the cognitive mechanisms used to adapt to a changing world. To address this, we developed a decision-making paradigm that allowed us to determine what strategies and biases emerge when humans detect a change in the environment and initiate a search for new rewarding options. The task required subjects to choose from a continuous, circular distribution of oriented lines, one of

which was at the center of a latent probabilistic reward distribution. The reward distribution would occasionally rotate, requiring subjects search for the new best orientation. We developed a regime-switching hidden Markov model to infer the subjects' goal state on each trial following change points: whether they were still choosing the previous best option, searching for a new option, or choosing the new best option. Across 3 separate experiments, we found that humans responded to change points largely through initiating a period of randomized, undirected search—despite the opportunity for more efficient, organized search strategies. Moreover, while in the search regime, subjects' decisions were more influenced by low level perceptual biases that were shared across observers and belief states. In other words, they used more bottom-up and less top-down control. Multiple types of bottom-up, perceptual biases were increased—including the bias for stimulus contrast, which was task-irrelevant—and only bottom-up biases were increased. Although other, non-perceptual biases were stronger overall (e.g. the preference for specific spatial locations), these biases were not enhanced during the search regime. Together, these results suggest that humans can make more flexible decisions by transiently reducing top-down control and reverting to bottom-up control. This strategy would randomize behavior with respect to current knowledge or beliefs—allowing new good actions to be discovered by accident—without compromising the hardwired attentional priorities selected for by evolution. Furthermore, analyses of pupil data from one experiment suggest that pupil size under constant luminance predicts the tradeoff between randomized and persistent decision-making and, at the same time, predicts the influence of low-level stimulus properties on gaze and decision-making. These results implicate pupil-linked mechanisms (such as norepinephrine and/or autonomic arousal) in regulating the tradeoff between persistent, controlled goal states and periods of flexible and responsive decision-making.

Disclosures: B.A. Ebitz: None. **J.D. Cohen:** None. **T. Buschman:** None.

Poster

088. Computational Models of Decision Making

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.03/TT28

Topic: H.02. Human Cognition and Behavior

Support: R01MH105452

Title: Changing maladaptive decision making through behavioral intervention: Implications for eating disorders

Authors: *E. HARTNETT[1], A. BAKKOUR[1], T. SCHONBERG[2], B. WALSH[3], K. E. FOERDE[3], J. STEINGLASS[3], D. SHOHAMY[1]
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Abstract: Anorexia Nervosa (AN) is characterized by persistent and maladaptive decisions about food, yet little is known about the basic decision making mechanisms that guide food choice in individuals with AN or how to change them. Specifically, individuals with AN choose low calorie, low fat foods, to the point of starvation, resulting in a mortality rate among the highest of any psychiatric illness. Changing decisions in AN is particularly challenging even when they know the risks involved. Indeed, food choices in AN appear to have both behavioral and neural markers of the sort of engrained habits that are particularly difficult to change, even among healthy individuals. To address this challenge, we leverage recent findings from decision neuroscience that elucidate the behavioral and neural mechanisms by which food-related choices can be modified in healthy individuals, and apply them to studying food choices in AN. Specifically, prior studies in healthy individuals demonstrated a long-lasting shift in food choice preference in healthy participants following a training paradigm, the cue-approach training task (Schonberg et al., 2014) that does not rely on external reinforcement. In this task, participants first rate how much they like foods. Then, individual food images are presented and participants are trained to press a button as fast as they can when they hear an auditory cue. The cue and button press are consistently paired with some of the items. Subsequently, participants choose between pairs of food items with similar initial ratings: one item associated during training with the cued button press (Go item) and one that was not (NoGo item). Given that ratings are matched in pairs of interest based on the baseline preference, absent of any effect of training, participants would be expected to choose Go and NoGo items equally often. Here, we used this training task in a group of patients with a confirmed diagnosis of AN and in a comparison group of healthy controls. Replicating prior work, we found that healthy controls choose Go over NoGo items, indicating that the cue approach training changed food choices. Interestingly, we found the same effect in the AN group, suggesting that even in this population the cue approach task led to a change in food choice. These findings suggest that food choices among individuals with AN can be modified in a similar fashion to what has been observed in healthy controls. Notably, this training task changes food choices without any external reinforcement and after one hour of training. Ongoing studies are exploring the mechanism by which the cue approach task modifies choices, whether through attentional processes or by modifying value per se.

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Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.04/TT29

Topic: H.02. Human Cognition and Behavior

Title: The double subject fallacy: Neuroscience, closet dualism, and defendant culpability

Authors: *K. SITA[1], *K. SITA[1], U. MAOZ[2], L. MUDRIK[3], J. J. A. VAN BOXTEL[4], G. YAFFE[5]
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Abstract: Neuroscience evidence is increasingly used in courtrooms, often by defense lawyers for very serious offenses using the "my brain made me do it defense". Their typical claim is that abnormalities in the defendant's brain made the defendant more likely to commit the crime. This defense is predominately used in the sentencing phase of the trial. However, a recent publication suggests that the claim "my brain made me do it," is inherently dualistic by treating the brain and the individual as two independent entities that can simultaneously occupy divergent psychological states. This dualistic claim conflicts with the materialistic perspective neuroscientists typically endorse. This phenomenon is termed the double-subject fallacy (DSF; Mudrik & Maoz, 2014). The present study aims to measure the effect the DSF has on perceived culpability in criminal court cases involving bodily harm. In the first experiment 609 Amazon Mechanical TURK (mTURK) participants were presented with a vehicular assault scenario. The scenario was manipulated between subjects to suggest that the defendant was guilty, innocent, or that his innocence is unclear (cupability). Additionally, neuroscientific evidence was presented either using DSF language ("The defendant's brain makes him have aggressive feelings more often than most people") or non-DSF language ("The defendant has aggressive feelings more often than most people"). Perceived culpability was measured on two 7-point Likert scales, and participants were instructed to indicate the extent to which they agreed that the defendant intended to kill the victim, and to indicate a recommended jail sentence (in number of months) for the defendant. An ANOVA suggested a significant main effect of culpability, validating the manipulation of our independent variable. Critically, there was an additional main effect of DSF usage, such that when DSF language intent to kill ratings were significantly lower than when DSF language was not used, with no significant interaction. In a second experiment, we will run 1794 additional mTURK participants using a bodily harm scenario. Here again, we presented expert testimony either using DSF language or non-DSF language. The effect of the DSF on the perceived culpability of was replicated here. These combined results reveal that defendants were perceived as having less intent to kill the victim when the neuroscientific evidence in the case was presented using DSF language, regardless of our culpability manipulation. This suggest that DSF language may have real consequences in how people interpret culpability, which may influence courtroom outcomes.

Disclosures: K. Sita: None. **U. Maoz:** None. **L. Mudrik:** None. **J.J.A. van Boxtel:** None. **G. Yaffe:** None.

Poster

088. Computational Models of Decision Making

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Program#/Poster#: 088.05/TT30

Topic: H.02. Human Cognition and Behavior

Support: NSF 1533623

Title: Optimal prediction strategies in noisy and changing environments

Authors: *G. TAVONI, T. DOI, C. PIZZICA, V. BALASUBRAMANIAN, J. I. GOLD
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Abstract: To thrive in a noisy and dynamic world, it is important to learn from past experiences to make effective predictions about future events. In environments that include unpredictable and unsignaled change-points that render past experiences irrelevant to future predictions, this learning process must be adaptive to take into account only the most-relevant information. We showed previously that this kind of adaptive process can, under certain assumptions, be approximated by a probabilistically weighted combination of delta-rules that each minimize prediction errors based on a particular time constant of integration over past events. Here we tested whether, at lower signal-to-noise (S/N) levels, prediction strategies become less adaptive and whether they may be explained by a delta-rule model with a single integration time constant, or by an even simpler model with no memory of past history. We focused on a task in which human subjects see a series of events (dots) drawn from a Gaussian distribution with a fixed variance and a variable mean that undergo change-points at fixed rate h. The ratio between the variance of the generative mean and the variance of the samples given a fixed mean defines the S/N of the process. The delta-rule model is defined by the prediction rule $P(t)=P(t-1)+\alpha(X(t)-P(t-1))$, where α is the learning rate and $1/\alpha \sim$ integration time scale of past history. The memory-less model is defined by the prediction rule $P(t)=\beta*prior+(1-\beta)*X(t)$, where the prior is taken as the average position of dots in the observation phase, and β and $(1-\beta)$ are the weights given to the prior and to the last observed data point, respectively. We fit these two models to experimental data and compared the empirical values of α and β with the optimal values computed analytically by minimizing the average prediction error for different values of h and S/N. Optimal values of α have a non-monotonic dependence on h and do not seem to capture the empirically measured values. Conversely, empirical values of β match qualitatively the optimal values, increasing linearly with h, with S/N-dependent slope and y-intercept. These preliminary results suggest that in regimes of low S/N, the complexity of human prediction strategies is reduced substantially compared to high S/N regimes, which were the typical focus of previous studies. In these low S/N regimes, the adaptiveness of the prediction strategy and the working-memory load are both reduced to a minimum, and decisions are determined primarily by weighing the prior and the last

observed data point. Individual differences are also observed, with different people spanning different ranges of β values as the S/N is varied.

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Poster

088. Computational Models of Decision Making

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Program#/Poster#: 088.06/TT31

Topic: H.02. Human Cognition and Behavior

Support: NIH F32MH102009

Title: Behavioral and EEG signatures of hierarchical evidence accumulation

Authors: *M. R. NASSAR[1], J. S. KIM[2], M. J. FRANK[3]
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Abstract: Over the past 25 years, neuroscience and psychology research has shed considerable light on how people make simple perceptual decisions. When perceptual information is ambiguous, people tend to accumulate noisy information over time until reaching a “threshold” of certainty about the underlying stimulus before committing to a categorical action. However, in real world perceptual decision problems, the best course of action often depends on a fairly complex set perceptual features - for example, a decision to turn right at an intersection might depend on the color of the traffic light as well as the presence and location of oncoming traffic. To reduce the processing load necessary to solve this sort of complex problem, it can be beneficial to construct hierarchical decision trees that eliminate the need to process irrelevant features - for example, after accumulating sufficient evidence to conclude that the traffic light is green one should look for oncoming traffic across the intersection, whereas if it is red one should look for oncoming traffic to the left. In either case, by first focusing on the color of the traffic light, the number of perceptual categorizations necessary to choose the best course of action can be reduced. Here we examine whether and how people exploit this sort of structure to facilitate efficient decision making using a perceptual decision task that incentivizes hierarchical strategies for accumulating information about multi-attribute sensory stimuli. On each trial, one of three ambiguous feature dimensions (motion, color, orientation) would dictate which of the other dimensions was necessary for determining the correct response. Analysis of simulated and actual task data suggests that subjects processed stimulus dimensions serially in order of their position on a hierarchy (e.g., assessing the color of the traffic light before the presence of oncoming traffic), while also invoking an urgency signal. Together, these computational features capture a

tendency for errors in categorizing low (but not high) stimulus dimensions to increase as a function of reaction time. Simultaneous EEG recordings allowed us to assess potential asymmetries in the neural representation of stimulus features at different time points. We use these EEG-based measures of feature representation to inform and test candidate models of hierarchical processing of perceptual features for efficient decision making.

Disclosures: **M.R. Nassar:** None. **J.S. Kim:** None. **M.J. Frank:** None.

Poster

088. Computational Models of Decision Making

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Title: Effort-reward decision-making in math anxious individuals

Authors: ***K.-W. CHOE**, C. S. ROZEK, J. BRAXTON, M. G. BERMAN, S. L. BEILOCK
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Abstract: Many individuals report strong feelings of tension, apprehension, and fear of math (Richardson and Suinn, 1972). This emotional reaction, termed math anxiety, has long been hypothesized to be associated with avoidance of math-related situations, coursework, and STEM careers (Hembree, 1990; Ashcraft & Ridley, 2005). However, little research has directly investigated the relationship between math anxiety and math avoidance. We devised a novel decision-making task requiring a trade-off between monetary reward and cognitive effort for solving a math or a word problem. On each math (or word) trial, participants were asked to choose between a low-effort option, which always offered 2 ¢, and a high-effort option, which offered 2, 3, 4, 5, and 6 ¢, e.g., Easy Math 2 ¢ vs. Hard Math 6 ¢. After this selection participants solved a presented math (or word) problem based on their previous selection. Participants were also given accuracy feedback after each trial. 141 participants were recruited from the Amazon Mechanical Turk online labor market and completed 100 randomly interleaved math and word

trials (200 trials total); receiving a monetary reward for the problems they solved correctly. Low-effort problems were solved more quickly and accurately (RT: math 2.23±0.43 s, word 2.16±0.31 s; accuracy: math 95.4±6.0 %, word 93.6±6.3 %; M±SD across Ps) than high-effort problems (math 3.79±0.83 s, word 3.07±0.62 s). Importantly, the difficulty of those problems was continuously calibrated to a target accuracy of 71% regardless of individual differences in math and verbal competence. This was done using a 2-up-1-down staircase method and a large pool of problems sorted by 7 difficulty levels (problem counts: 1972 math, 1832 word). The resulting accuracy was 64.3±17.6 % for math and 68.8±9.3 % for word. The expected value of the high-effort options that offer 4, 5, and 6 ¢ was higher than that of low-effort options. When comparing participant math anxiety score (sMARS: 2.08±0.82) to probability of choosing the high-effort options that offered 4-6 ¢ in the math and word trials (60.3±40.8 % and 80.0±31.1 %, respectively), the higher one's math anxiety, the less likely they chose the high-effort options in the math trials ($r=-.35$ [-.49, -.20], $p<.001$), but not in the word trials (ANCOVA $F=10.9$, $p=.001$). Math anxious individuals are less willing to exert cognitive effort in math-related situations, even when there are high rewards for doing so.

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Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.08/TT33

Topic: H.02. Human Cognition and Behavior

Support: Brain/MINDS from AMED

Title: A Bayesian psychophysics model of a hierarchical sense of agency

Authors: *R. LEGASPI, T. TOYOIZUMI
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Abstract: Sense of agency (SoA) accounts for the self as the initiator of its own actions in order to interact with and influence the external environment. Here we introduce a theoretical model of SoA. Specifically, we theorize SoA as the correlation between our perception of the physical contiguity of an action and its outcome and our psychological experience, i.e., feeling and judgment, of the agentic origin of the action. The action and outcome are contiguous if their sequential occurrence or proximity causes their association in the brain. Our theory is consistent with the notion that the representational content of SoA is not only based on whether the self (or another) authored the action, but on the estimated causal relation between action and outcome as well. We employed a Bayesian inference model to estimate the experience of agency and the

perception of action-outcome contiguity. We adapted a model (in Sato, Toyoizumi and Aihara, Neural Computation 2007) that was originally used to explain the ventriloquism effect, which is an example of the brain perceiving two cues as coming from a common source. In the original model, the Bayesian observer estimated the original position and timing of audiovisual cues and simultaneously judged whether they are coming from the same source or not. We posit that perception of agency involves the brain simultaneously estimating whether the action and outcome are contiguous and the action was indeed caused by the self, which is therefore the common source. Hence, we looked at SoA through the same lens that the ventriloquism effect was viewed.
The second aspect of our theory is that SoA is hierarchical, i.e., our experience of agency and perception of action-outcome contiguity occur at two levels, with the higher level processes manifesting explicit conscious efforts and the lower level processes occurring even when we are not consciously reflecting. We extended our Bayesian inference model to account for this aspect. To demonstrate our theory and model we revisited the seminal report on intentional binding, which remains to be a compelling indirect measure of sense of agency. The binding effect was deemed "intentional" since it was a conscious aspect of a temporal linkage between representations of actions and outcomes. We hypothesize that certain mechanisms could have also occurred at the lower level, perhaps what we can call as the "unconscious" binding.

Disclosures: R. Legaspi: None. **T. Toyoizumi:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

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Program#/Poster#: 088.09/DP12/TT34 (Dynamic Poster)

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 MH098023

Title: Dopamine, prefrontal cortex, and strategic reasoning

Authors: *Z. ZHANG[1,3], I. SAEZ[2], M. HSU[1,2], A. KAYSER[3,2,4]
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Abstract: Social interactions are critically important to humans, making the acquisition of social strategies or heuristics in a given social context fundamental to daily function. Variations in the gene encoding catechol-O-methyl transferase (COMT), the enzyme primarily responsible for dopamine catabolism in the prefrontal cortex, have been shown to modulate learning in strategic games (Set et al., 2014, *PNAS*). However, the causal role of dopamine in specific aspects of

social decision-making remains to be established. Using a combination of pharmacological tools and economic games, we provide critical evidence for a causal involvement of dopamine in social learning and decision-making in the context of strategic interactions.
Across two sessions, healthy volunteers (N = 24) participated in the patent race, a social game in which two competitors bid to develop a new product, while they received either the brain penetrant COMT inhibitor tolcapone or placebo in a within-subject, randomized, double-blind, crossover design. We investigated the causal relationship between dopaminergic mechanisms and two critical aspects of learning: (i) reinforcement-based learning (RL), and (ii) belief-based learning through anticipating and responding to the actions of others. In order to capture behavior in multiple ways, we analyzed the data using both a computational model that explicitly incorporates RL and belief-based learning, and a regression that is agnostic with respect to mechanism. Although we remain blinded to the identities of the two treatments, participants differed across drug conditions in the degree to which their decision in the current trial depended on the opponent's decision in the previous trial ($p = 0.002$), a behavioral signature of belief-based learning. Furthermore, the formal computational model showed a significant difference in the parameter lambda, which captures reward sensitivity, between the two treatments ($p = 0.01$). These results support and extend the insights from previous human genetics (Set et al., 2014) and neuroimaging (Zhu et al., 2012) data using the same behavioral paradigm and modeling methodologies. These findings suggest a causal relationship between neurochemical systems and strategic social reasoning, and have potential implications for better understanding social impairments in neuropsychiatric disorders involving the dopaminergic system.

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Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.10/TT35

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust

Title: Dopamine modulates both option generation and creativity in behaviour

Authors: *Y. ANG, S. MANOHAR, O. PLANT, C. LE HERON, M. HUSAIN
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Abstract: Decision-making tasks typically ask people to select from two or more options generated by the experimenter, rather than requiring participants to generate options themselves. Several lines of research suggest that brain mechanisms underlying *self-initiated* actions differ from those involved in externally-triggered ones. It has recently been proposed that deficits in

self-initiated behaviour might underlie paucity of action in apathetic individuals, with dopamine playing a key role in modulating such behaviour. However, another body of work suggests that dopamine might affect creativity or flexibility in the ability to alter behaviour. Here, we first investigated in healthy people whether ability to generate *self-initiated* action options during decision-making relates to behavioural apathy and/or creativity (N = 96). Then we examined how these factors were influenced by dopamine, in patients with Parkinson's disease ON and OFF dopaminergic medication (N = 35). We developed a novel measure of option generation using variants of a touchscreen computer task. Participants were required to draw, in four minutes, as many different paths as possible between two fixed points. We quantified movement trajectory parameters as well as the novelty of options generated. Healthy people showed a trade-off between the number of paths they generated and the novelty of these options. Furthermore, although apathetic people initiated fewer paths, the options they generated were actually more creative. Parkinson's patients generated significantly more options when ON compared to OFF dopamine. Nevertheless, when OFF their medication, patients exhibited significantly greater mean novelty in their generated paths. Healthy age-matched controls were both fluent and creative, generating a comparable number of options to patients ON dopamine and exhibiting comparable creativity to patients OFF dopamine. Three control studies revealed that reduced option generation when OFF dopamine is not explained simply by (i) movement speed or executing actions, (ii) in planning and initiating actions, or (iii) in selecting amongst generated options. These findings offer new insight into decision-making when people have to generate options for *self-initiated* actions. They demonstrate that there may be a complex relationship between the ability to generate options and behavioural apathy versus behavioural creativity. Moreover, dopamine may play a key role in modulating the balance between producing more options versus generating more novel behavioural outputs.

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Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.11/TT36

Topic: H.02. Human Cognition and Behavior

Title: Dorsal anterior cingulate-midbrain ensemble as a reinforcement meta-learner

Authors: *M. SILVETTI[1], E. VASSENA[2], T. VERGUTS[1]
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Abstract: The dorsal anterior cingulate cortex (dACC) plays a pivotal role in higher-order cognition. Currently, the three main theoretical frameworks attempting to capture the elusive computational nature of this brain area are Reinforcement Learning (RL), Bayesian decision-making, and cognitive control. Although theoretical effort to explain the dACC functions is intensifying, no theoretical framework managed so far to account for all the relevant experimental data. Here we propose that dACC plays, controlling midbrain catecholamine nuclei, the role of a reinforcement meta-learner. This cortical-subcortical system not only can learn and make decisions based on action-outcome comparisons, but it can also learn to control performance and learning process itself, for both its own circuits and for other brain areas. We implemented this theory in a neural model, the Reinforcement Meta-Learner (RML), and simulated an unprecedented number of experimental findings, including volatility estimation, effort exertion, higher-order conditioning and working memory. The RML implements meta-learning by means of approximate Bayesian learning (at computational level) and respecting several neuro-functional and neuro-anatomical constraints (at biological level). These features provide a perspective that assimilates the other theoretical proposals in a single (neurophysiologically-based) computational framework that can generate mechanistic explanations and experimental predictions at both behavioural and neurophysiological level.

Disclosures: M. Silvetti: None. **E. Vassena:** None. **T. Verguts:** None.

Poster

088. Computational Models of Decision Making

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Support: Presidential Scholars in Society and Neuroscience Faculty Seed Grants for Interdisciplinary Projects in Society and Neuroscience (PSSN), Columbia University

Research Initiative for Science and Engineering (RISE), Columbia University

Title: Non-normative information sampling in humans

Authors: *K. KOBAYASHI, Y.-N. JEON, A. BARANÈS, S. RAVAIOLI, M. WOODFORD, J. GOTTLIEB
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Abstract: In natural behavior, decision makers (DM) gather information by actively sampling relevant cues. It is known that humans are motivated to sample information even when it is non-instrumental, i.e., they cannot change their future actions to improve outcomes. Although active information sampling is ubiquitous, it has been eschewed in laboratory paradigms in which

participants typically make decisions based only on experimenter-selected cues, and very little is known about the logic of information sampling policies: which factors determine how much interest we ascribe to competing relevant cues? To examine this question, we investigated how humans choose among multiple sources of information pertaining to a single future monetary outcome. Participants (n = 142) completed a paradigm in which they were given rewards based on the sum of random draws from two independent lotteries that differed in their variance and expected value (EV). The participants could not influence the payoffs they earnt, but were asked to choose the lottery whose prize they wished to reveal; upon declaring her choice, the DM was shown the precise prize drawn from the chosen lottery, while the remaining prize was only revealed at the experiment's end. Information choices were sensitive both to the variance and EV of the individual lotteries. A subset of participants consistently chose to obtain information about the larger variance lottery independently of EV, consistent with a preference for the early reduction of uncertainty. However, a majority were also strongly or exclusively sensitive to EVs, choosing to learn about the higher EV lottery even when it had lower variance. The effect of EV is at odds with normative economic models postulating that DM should only seek to reduce uncertainty about the total outcome (a quantity that is insensitive to the EV of an individual lottery). The findings suggest that humans are biased to sample information about aspects of a situation that are individually salient or desirable, but not necessarily most informative about the utility to be obtained from the future outcome. In ongoing experiments we examine the robustness of these findings in conditions involving monetary costs and instrumental sampling strategies.

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Poster

088. Computational Models of Decision Making

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Title: Time preferences are reliable across time-horizons and verbal vs. experiential tasks

Authors: Y. WANG[1], E. LUKINOVA[1], J. MOLLER-MARA[1,2], S. F. LEHRER[1,3,4], *J. C. ERLICH[1,5]
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Abstract: Individual's intertemporal preferences between larger delayed rewards and smaller immediate rewards in the lab are viewed to be predictive of important life outcomes, such as SAT scores, graduating from college, and overall income. Moreover, a strong preference for immediate rewards (so called "impulsivity") is often linked with anti-social behaviors like drug abuse and gambling addiction. For these reasons, intertemporal choice in both humans and animals is widely studied by economists, psychologists and neuroscientists. However, there is a two significant gaps between the methods used to study intertemporal choice (also called delay discounting or temporal discounting) in animals and those used in humans. In animal studies, tasks are non-verbal and animals have to wait for reward on each trial to experience the delay, so the delays are short (< 1 minute). In human studies, subjects are asked questions like "Would you rather have $10 today or $15 in one month?". Thus, there are two substantial gaps between animal and human methods of estimating discount factors: short vs. long times and nonverbal or "experiential" vs. verbal choice description. We aimed to bridge the gap between human and animal temporal discounting research by measuring the discount factors of human subjects in three ways. First, we used a novel language-free task for humans that is identical to a task that we also use to train rodent subjects. Second, we tested subjects using a verbal task, but using the same short (< 2 minutes) time scales as in the non-verbal task. Finally, we tested subjects using the standard verbal task with time-scales spanning days to months. This design allowed us to test whether a single process was used for intertemporal choice regardless of time-horizons or verbal vs. experiential situations, or whether the choices in different settings would be better explained by distinct underlying mechanisms. We found that the rank of the subject's impulsivity across the three measures was relatively consistent, with the rank correlation between non-verbal and short-verbal and between short-verbal and long-verbal settings to be around 75% of the correlation that would be expected if subjects used a single discount factor for all three settings. This novel within-subject design validates the use of non-verbal tasks to study the neural mechanisms of intertemporal choice across humans and animals.

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Poster

088. Computational Models of Decision Making

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Topic: H.02. Human Cognition and Behavior

Support: LabEx Bio-Psy grant to AW

Title: The computational role of executive control in economic decisions

Authors: *A. WIEHLER, I. T. KURNIAWAN, J. DAUNIZEAU, M. PESSIGLIONE
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Abstract: The ability to resist the temptation of immediate rewards, when opposed to larger but delayed rewards, is an important predictor of higher education and professional success. This ability has been related to the intervention of the fronto-partial executive control network, including the lateral prefrontal cortex (lPFC). Indeed, reduced activity in the lPFC has been associated with more impulsive choices - i.e. higher propensity to select immediate rewards (Figner et al., 2010; Blain et al., 2016). However, the precise role of executive control in economic decision-making is still poorly understood at the computational level. Standard accounts simply state that executive control is necessary for suppressing the impulse to take immediate rewards.Here, we suggest an alternative and more formal account: Executive control is needed to integrate multiple features of choice options, such as reward magnitude and delay in the case of inter-temporal decisions. More technically, exerting executive control would improve the precision of scaling parameters in the value function that integrate the different features of a choice option. Conversely, value estimates of multidimensional options would remain more uncertain when executive control is reduced. As a consequence, since people tend to avoid uncertain estimates, they might shift their choice towards options which require less feature integration, e.g. immediate rewards. In addition to the computational model, we present validation studies in healthy participants that manipulate the level of executive control invested in economic decision-making. Three types of manipulations have been implemented: time pressure (upper limit for committing to a choice), dual-tasking (making choices while maintaining speed on a bike) and fatigue (prolonged exertion of executive control). We also extend our theory beyond inter-temporal choice by testing risky choice, where dimensions are reward magnitude and probability (with sure options being the equivalent of immediate rewards). Our findings regarding the role of executive control could, therefore, generalize to many forms of economic decisions which involve the integration of multiple dimension.

Disclosures: **A. Wiehler:** None. **I.T. Kurniawan:** None. **J. Daunizeau:** None. **M. Pessiglione:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.15/TT40

Topic: H.02. Human Cognition and Behavior

Support: Hong Kong Research Grants Council 25610316

Wellcome Trust

Title: Local and global effects of irrelevant options on decision making

Authors: *B. K. CHAU[1], C. LAW[1], M. F. RUSHWORTH[2,3]
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Abstract: In multiple choice decision making, there has been considerable interest in how varying the value of a third, irrelevant option could have an impact on choices. Intriguingly, opposite predictions are made by two classes of decision models. An attractor network model that is biophysically plausible suggested that larger values of the third option should be associated with more optimal choices and stronger signals in the ventromedial prefrontal cortex (vmPFC). In contrast, a divisive normalization model that has been successful in describing neural activity in visual regions makes opposite predictions - larger third option values are related to less optimal choices and weaker signals in the parietal cortex. Despite the opposite behavioral predictions of the two models, it is possible that they are associated with different aspects of decision making. In this study, we combined data from multiple experiments that involved different variants of a three-option decision making task. In all the versions, one of the options was assigned as an unchoosable distractor and participants had to choose between the remaining two options. The behavioral analysis showed that when the distractor value was large participants made more optimal choices, which was consistent with the attractor network model predictions. Intriguingly, the analysis also showed that larger total values of the three options were associated with poorer decision making, which was consistent with the divisive normalization predictions. Furthermore, previous studies suggested that decision making signals in vmPFC are modulated by attention. It is possible that the “attractor network” effects of the distractor were associated with specific eye movement patterns. Eye tracking data from one of our experiments suggested that more optimal choices were made when there was a large proportion of fixations at the distractor as well as gaze transitions between the distractor and the optimal option. These findings concurred with the activity in vmPFC obtained from a functional magnetic resonance imaging (fMRI) experiment. Our data suggested that larger values of the third option were associated with stronger “local” attention-guided effects that led to more optimal decision making but also with “global” normalization effects that led to poorer decision making.

Disclosures: **B.K. Chau:** None. **C. Law:** None. **M.F. Rushworth:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: MOST 104-2410-H-010 -002 -MY3

Title: Context effects on subjective probability and choice under risk

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Abstract: Considerable evidence suggests that value-based decisions are highly sensitive to context. The vast majority of studies on context-dependent value computations focused on situations where there is no uncertainty involved. It remains an open question as to how context impacts value computations in the domain of probability of reward. In this study, we systematically manipulated the reward probabilities and measured participants' subjective probability and choice to investigate how experience shapes context-dependent computations under uncertainty.
Method. In a simple stimulus-outcome association task, subjects were instructed to learn the probability of reward associated with different visual stimuli. In each trial, subjects were presented with one stimulus and required to indicate their estimate of its reward probability by pressing buttons. After a response was made, an outcome was presented, showing whether they received a monetary reward. Each block consisted of two stimuli associated with different probabilities of reward. The experiment included six different stimuli; they were equally assigned to three different probabilities of reward: 10%, 50% and 90%. Context was manipulated by pairing stimuli carrying the same probability of reward with stimuli carrying different probabilities of reward in different blocks of trials. In order to examine whether context would impact choice behavior, after the stimulus-outcome association task, subjects performed a choice task in which they were instructed to choose between pairs of stimuli experienced in the association task.
Results. Twenty subjects participated in the experiment. We found that context had an impact on subjective probability and choice. However, this impact was not universally observed across the entire range of probability. Only 50% chance of reward showed significant context effect on both subjective probability and choice. Subjects gave larger estimates when the 50%-reward stimulus was experienced with a 10%-reward stimulus than with a 90%-reward stimulus. When choosing between the two stimuli both carrying 50% chance of reward, subjects preferred the stimulus experienced with a 10% chance of reward than that experienced with a 90% chance of reward. Preliminary fMRI data suggested that the dorsomedial prefrontal cortex (dmPFC) represent the

context value - its activity correlates with the expected value of block. Furthermore, dmPFC activity represents both the direction and degree of context effects, indicating its role in context-dependent computations for subjective probability.

Disclosures: W. Shih: None. **S. Wu:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

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Program#/Poster#: 088.17/TT42

Topic: H.02. Human Cognition and Behavior

Support: MOST 104-2410-H-010-002-MY3

Title: Endowment effect on risk? Testing the stochasticity of reference point in decision under risk

Authors: *S.-Y. CHANG[1], C.-I. YEH[2], S.-W. WU[3]
[2]Dept. of Psychology, [1]Natl. Taiwan Univ., Taipei, Taiwan; [3]Inst. of Neurosci., Natl. Yang-Ming Univ., Taipei, Taiwan

Abstract: The endowment effect is a tendency to value a good more when owning it. This effect has been attributed to loss aversion caused by a change in reference point. Köszegi and Rabin (2006) proposed a model that specifically defines reference point as expectations and that are stochastic in nature. However, the empirical evidence for the model remains controversial. One possibility for inconsistent findings is the effectiveness of the endowment manipulation. To address this question, in this study, we designed a novel lottery decision task. Thirty subjects participated in the experiment (female=15). Each subject went through 72 trials. In the beginning of each trial, the subjects were first endowed with a lottery on one side of the monitor (left or right), and then was given a new lottery on the other side. The new lottery differed from the endowment in reward probability (±5%, ±10%, ±15%) and expected value (0, ±2 coins). Subjects had to decide whether to keep the endowment or choose the new lottery. In both cases, the chosen lottery became the endowment on the next choice problem. The subjects faced up to 6 choice problems on each trial. At the end of the experiment, one trial was selected at random and the chosen lottery was realized. First, we found that subjects tended to keep the lottery endowed by their own choice but not the endowment initially given. This suggests that the endowment effect is mediated by the degree of ownership. Second, consistent with the prediction of Köszegi and Rabin's model, the endowment effect (the frequency of keeping the endowed lottery) was affected by the probability of reward associated with the endowed lottery. This effect was mediated by the difference in probability of reward between the lotteries. That is, subjects become more risk averse/seeking when endowment had a higher/lower reward probability. In

summary, these results indicate that reference points are stochastic, and that a greater sense of ownership enlarged the endowment effect.

Disclosures: **S. Chang:** None. **C. Yeh:** None. **S. Wu:** None.

Poster

088. Computational Models of Decision Making

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Title: Modifying the magnitude of stimulus noise can distinguish between neural mechanisms of evidence integration

Authors: *G. PRAT ORTEGA[1,2], K. WIMMER[4,3], N. WILMING[5], T. H. DONNER[6], A. C. ROXIN[7], J. DE LA ROCHA[8]
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Abstract: The integration of sensory evidence in perceptual 2-Alternative Forced-Choice (2AFC) tasks has been studied extensively and yet establishing a unifying neural mechanism has remained elusive. Because various models based on different mechanisms can typically account for the dependence of performance and reaction time on mean stimulus evidence, we derived and tested disambiguating predictions about the impact of stimulus noise on the decision. We studied the dynamics of an attractor network model and compared them with other phenomenological integration models (e.g. uniform integration).

To this end, we considered a stimulus in which the evidence is drawn in each time step from a distribution with mean ±m and standard deviation s, the sign of m determining the stimulus category. The dynamics of the attractor model can be summarized in a double-well energy landscape in which m makes deeper the correct well. The stimulus noise plus the brain intrinsic noise leads to stochastic transitions between wells. Analytical and numerical analysis of these transitions yielded two results: (1) As s increased, the stimulus samples with a higher impact on choice shifted from the beginning (transient integration or primacy) to the end of the stimulus (leaky integration or recency). With small s the first visited attractor determined the final choice whereas for higher s there were transitions between wells and the choice was then determined by the last transition. (2) We found a range of s where the benefit of having more correcting than error transitions offset the decrease in signal-to-noise ratio due to higher s. Thus performance showed a non-monotonic dependence with s with a local maximum at $s_{max} > 0$. Importantly, other models that considered uniform evidence integration yielded qualitatively different predictions.
To test these predictions we collected behavioral data from sixteen human subjects performing a 2AFC visual task. We interleaved trials with 6 different s and the same m. Preliminary behavioral analysis showed that psychophysical kernels in most subjects tended to show primacy for all values of s (a few subjects exhibited recency kernels). For most subjects performance stayed constant for small to intermediate levels of s and decayed at high s. Some subjects showed a non-monotonic behavior with a local maximum at a non-zero s, as predicted by the theory. Given the heterogeneity across subjects we aim to fit a general potential capturing various dynamical features (attraction, leak, etc) to the behavior of each participant. This will allow us to quantitatively characterize the idiosyncratic differences in the dynamics of evidence integration across subjects.

Disclosures: G. Prat Ortega: None. **K. Wimmer:** None. **N. Wilming:** None. **T.H. Donner:** None. **A.C. Roxin:** None. **J. de la Rocha:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.19/TT44

Topic: H.02. Human Cognition and Behavior

Title: Musical Trailers: How do we sample and remember music?

Authors: *S. J. PHILIBOTTE, S. SPIVACK, N. H. SPILKA, I. J. PASSMAN, P. WALLISCH
Dept. of Psychology, New York Univ., New York, NY

Abstract: We are interested in how well we can predict whether individuals will like a song from their appraisal of a short clip taken from the song. This is important because past research

on musical preference only presented clips - not songs - raising the question whether the clips are representative. Here, we exposed 600 participants to music clips and songs. The 3120 clips were taken from various sections of 260 songs picked from a diverse range of genres. The clips were taken from different specified sections of the song (e.g. Intro, Chorus, Verse) and varied in duration from 5 to 15 seconds. Using this high powered sample, we can show that the correlation between clip and song rating is on the order of 0.94 and it did not matter much where in the songthe clip was taken or which genre the song came from. Surprisingly, this was true even for the 5 second clips. We conclude that individuals are rapidly able to ascertain how much they will like a given song, perhaps due to being able to identify whole genres they like or dislike. This research validates prior work on music using clips that were picked non systematically. In addition, it has implications for the necessary length of "musical trailers" as individuals are able to identify songs they will like in as little as 5 seconds - much shorter than the current industry standard.

Disclosures: S.J. Philibotte: None. **S. Spivack:** None. **N.H. Spilka:** None. **I.J. Passman:** None. **P. Wallisch:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.20/TT45

Topic: H.02. Human Cognition and Behavior

Title: High refresh rate allows early decision making

Authors: *M. POUJADE[1], F. GALLUPPI[2], Q. SABATIER[1], M. A. KHOEI[1], R. BENOSMAN[1]
[1]Inst. De La Vision, Paris, France; [2]Gensight Biologics, Paris, France

Abstract: Visual restoration devices such as retinal implants rely on vision sensors and the information acquired by such cameras is processed to produce visual stimulations. Therefore, the processing frequency is a key parameter of this pipeline.Most implants stimulate at typically low frequencies (tens of Hz), while according to experimental evidences retinal ganglion cells respond to highly dynamic stimuli with temporal precision of 1-10 ms.Our hypothesis is that stimulation frequency impacts the decision making process and optimizing this frequency can make the full process more ecological.This work seeks to assess the impact of the stimulation frequency on decision making.
Ten subjects performed a psychophysical task at varying frame rates using a projector with a maximum display frequency of 1440 kHz. The stimulation is made of randomly moving dots having varying velocity. A set (10%, 30% or 50%) of dots suddenly become coherent and move either to the right or the left. The subjects must immediately report to which side the dots move by pressing a button. Both the decision and the reaction time are recorded.

Beside the expected result that responses are more accurate and faster with the increase of the coherence, we demonstrate a diminution of 200 ms of the reaction time between a high frame (1440 Hz) rate and a low frame rate (60 Hz). No difference, both in the percentage of good response and reaction time, due to the velocity, was significantly observed.

Disclosures: **M. Poujade:** None. **F. Galluppi:** None. **Q. Sabatier:** None. **M.A. Khoei:** None. **R. Benosman:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

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Program#/Poster#: 088.21/TT46

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01DA038063

Title: Testing optimal evidence accumulation and time preferences in value-based decision making

Authors: *C. K. STEVERSON, H.-K. CHUNG, J. ZIMMERMANN, K. LOUIE, P. GLIMCHER
NYU, New York, NY

Abstract: Evidence accumulation models of decision making have been widely used to study behavior in a variety of tasks. The most well-known of these, the drift-diffusion model (Gold and Shadlen, 2007), has been shown to be optimal in a limited number of environments. Recently, growing attention has been paid to optimal evidence accumulation in a wider set of value-based choice tasks (Tajima, Drugowitsch and Pouget, 2016; Fudenberg, Strack and Strzalecki, 2017; Woodford, 2016). These optimal approaches share the feature that they depend only on the relative subjective value of the choice alternatives and are insensitive to the absolute level. This leads to the prediction that behavior is invariant to adding a constant amount of subjective value to each alternative, a prediction we refer to as *value-scaling invariance*. Notably, this prediction is shared by the valued-based version of the drift-diffusion model, but not by competing models of value-based choice such as normalization (Louie, Grattan and Glimcher, 2011).
We examine the theoretical aspects of the optimal evidence accumulation models that lead to value-scaling invariance. We conclude that this property depends on the form of the decision maker's time preference. Models that employ a flow cost of time where each second has a fixed opportunity cost (as in Tajima, Drugowitsch and Pouget, 2016; Fudenberg, Strack and Strzalecki, 2017) will generally lead to value-scaling invariance, while models that use discounting instead predict that a constant increase in subjective value should increase choice stochasticity and reduce reaction times. Notably, the predictions from the discounting model are in line with the

normalization model of decision making.
We are also experimentally testing the value-scaling invariance prediction on human subjects making choices over risky lotteries involving snack goods and money. In order to implement adding a constant subjective value to each choice alternative, we make use of the independence axiom and manipulate the probabilities of uncertain outcomes.

Disclosures: C.K. Steverson: None. **H. Chung:** None. **J. Zimmermann:** None. **K. Louie:** None. **P. Glimcher:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.22/TT47

Topic: H.02. Human Cognition and Behavior

Support: SFB TRR 169 “Crossmodal Learning: Adaptivity, Prediction and Interaction”

Title: A model combining reinforcement learning and self-evaluations explains how humans learn about character traits

Authors: *C. W. KORN[1], G. ROSENBLAU[2], J. GLÄSCHER[1]
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Abstract: In recent years, several variants of reinforcement learning models have been successfully extended to describe behavioral and neural mechanisms in social contexts. However, it is unclear if reinforcement learning can capture aspects of how humans learn about each other’s character traits (e.g., helpful, polite, and diligent). Character traits are interrelated and structured. Learning might be influenced by structures like the Big Five personality traits, a well-established classification of empirically identified commonalities and differences between personality traits. That is, persons may learn by generalizing across similar traits (i.e., if she is diligent she may also be hard-working). On the other hand, learning may be influenced by the learner’s notion of how much the traits characterize themselves. In a behavioral study, participants (n=36) were asked to consecutively predict how four other persons had previously rated themselves on a series of 60 trait words. After each prediction, participants received veridical feedback (but they never met the other persons). Participants also provided self-ratings on the same traits. Bayesian model comparison shows that a combination model provides the best and most parsimonious fit. This combination model weighs reinforcement learning (across character traits belonging to the same Big Five factor) with a reliance on participants’ self-ratings. Fine-grained model comparisons suggest that participants adjust the weighting factor in the combination model according to the person they are learning about. Overall, our results

indicate that a variant of a reinforcement learning algorithm can describe some of the dynamics that are at play when persons get to know each other.

Disclosures: C.W. Korn: None. **G. Rosenblau:** None. **J. Gläscher:** None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.23/TT48

Topic: H.02. Human Cognition and Behavior

Support: NSFC:31271169

NSFC:31671077

Title: Neural mechanism underlying risk attitude and probability distortion: One two-stage model of valuation and choice

Authors: *D. WANG
Sch. of Systems Science,Beijing Normal Universit, Beijing, China

Abstract: Although the neural mechanism underlying risk decision has been extensively investigated, the origination of risk attitude and probability distortion need to be further elucidated. In this study, the Rescorla-Wagner model with learning rates a_+/a_- upon gain/loss evaluates the risky reward and forms the subjective values of risky options through learning process, and the softmax function of subjective values produces the choice probability between options. Our model demonstrates that the combination of undervaluation or overvaluation of risky reward and the subjective risk (standard deviation of the subjective value) determine the risk attitude. Notably, our model predicts one reasonable new type of risk behavior: seeking small risk but avoiding large risk. Meanwhile, the asymmetric learning rates result in overweighting/ underweighting of small probabilities, suggesting that risk attitude and probability distortion share the same neural mechanism.

Disclosures: D. Wang: None.

Poster

088. Computational Models of Decision Making

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 088.24/TT49

Topic: H.02. Human Cognition and Behavior

Title: Forcing speeded responses inflates RT variance: A speed-stability tradeoff

Authors: *J. TEMAN[1], R. B. IVRY[2], I. GREENHOUSE[2]
[1]Psychology, [2]Univ. of California Berkeley, Berkeley, CA

Abstract: A large body of work has established a tradeoff between response time and response accuracy. However, it has recently been shown that people, when pressed, can respond faster than their voluntary RT without a loss in accuracy. This finding was interpreted as revealing a degree of independence between processes for motor preparation and motor initiation. We set out to explore this hypothesis using a two-alternative spatial discrimination task. Participants (n = 13) completed three conditions: 1) Free-RT, in which participants were encouraged to respond as quickly as possible after stimulus onset; 2) Forced-RT, in which participants were instructed to respond coincidently with the end of a countdown period: On each trial, the target was presented -300 to 0 ms (uniform distribution), relative to the end of a countdown period; 3) Pressured-RT, identical to the Free-RT condition, except that targets were visible for a limited time (2s, 800ms, 350ms, 300ms, 200ms, 186ms, or 100ms). To motivate fast RTs, in this condition, participants received negative feedback if they failed to respond before the target disappeared. Replicating the previous study, Free-RT (273 ± 90 ms) was slower than Forced-RT (224 ± 38 ms). However, unlike the previous study, Free-RT also tended to be slower than Pressured-RT (236 ± 56 ms). Moreover, the mean standard deviation of the RT distribution (calculated for each individual) was significantly smaller in the Free-RT condition (54 ± 31 ms) than in the Forced-RT (88 ± 23 ms) and Pressured-RT (72 ± 23 ms) conditions. Thus, while RT tended to be faster in the Forced- and Pressured-RT conditions than in the Free-RT condition, RT variance also increased. Even though previous work suggests response accuracy may not be compromised when faster responses are induced by time pressure manipulations, the variability of the RTs increases, indicating a different cost.

Disclosures: J. Teman: None. **R.B. Ivry:** None. **I. Greenhouse:** None.

Poster

088. Computational Models of Decision Making

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Program#/Poster#: 088.25/TT50

Topic: H.02. Human Cognition and Behavior

Support: NSF EPSCoR (RII Track-2 FEC)

Title: Pattern of response time reveals the construction of reward value during adaptive learning and choice

Authors: *S. FARASHAHI, K. ROWE, Z. ASLAMI, M. GOBBINI, A. SOLTANI
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Abstract: Every cognitive function involves various processing stages and computations, which are performed by fast synaptic transmissions and neural activity with little delay. Accordingly, the pattern of response time (RT) has long been used to infer neural processes underlying various cognitive functions including working memory, attention, and decision making. However, it is currently unknown if RT is also informative about various stages of value-based choice, and especially how reward values are constructed. To investigate this, we analyzed the pattern of RT during a multi-dimensional learning and decision-making task, which can prompt subjects to adopt different learning models. In our experiments, subjects could use reward feedback to directly learn reward values associated with alternative choice options (object-based learning). Alternatively, they could learn values of options' features (e.g. color, shapes) and combine these values to estimate the reward values for individual options (feature-based learning). Firstly, we found RT was strongly modulated by the difference in the value of reward probabilities or subjective values assigned to the two alternative objects on a given trial. Secondly, the number of dissimilar features between the two alternative options had opposite effects on RT depending on whether object-based or feature-based learning was adopted on a given trial and on the relationship between feature values and object values in the environment. Finally, RT reflected the model adopted by the subject on a trial-by-trial basis indicating an overall faster construction of reward value during object-based learning. Altogether, these results demonstrate that the pattern of RT can be used to infer how reward values are learned and constructed during adaptive choice.

Disclosures: S. Farashahi: None. **K. Rowe:** None. **Z. Aslami:** None. **M. Gobbini:** None. **A. Soltani:** None.

Poster

088. Computational Models of Decision Making

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Topic: H.02. Human Cognition and Behavior

Support: NSF CRCNS grant (BCS-1309346)

Title: Dependence of reward-based learning and decision-making on environmental statistics such as reward abundance and variance

Authors: *D. GUO[1], A. J. YU[2]
[1]Electrical and Computer Engin., [2]Cognitive Sci., UCSD, San Diego, CA

Abstract: Making repeated choices among multiple options in a noisy reward environment, such as in the multi-armed bandit task, provides an opportunity to study how the brain learns about reward statistics based on sequential observations, as well how it makes choices that negotiate a trade-off between exploitation (selecting the arm currently perceived to be most rewarding) or exploration (selecting an arm associated with greater uncertainty). Here, we manipulate the statistics of the task environment, specifically average reward abundance and variance, to examine how they modulate human reward-based learning and decision-making strategy. We use a Bayesian model comparison and parameter fitting framework to characterize the nature of statistical representation for learning and decision-making, as well as the relative prioritization of immediate reward, cumulative reward, and pure information (related to curiosity), on an individual basis. We find that there is substantial variability across individuals in both the complexity and parameterization of their learning and decision-making strategies.

Disclosures: D. Guo: None. **A.J. Yu:** None.

Poster

089. Individual Differences

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 089.01/TT52

Topic: H.02. Human Cognition and Behavior

Title: Psychopath aesthetics: Musical preference as an indicator of psychopathy scores

Authors: *N. A. LEAL[1], P. WALLISCH[2]
[1]Neural Sci., [2]Ctr. Neural Sci., New York Univ., New York, NY

Abstract: Emotional, social and cognitive aspects of psychopathy are relatively well understood. In contrast, little is known about the aesthetic preferences of psychopathic individuals. Psychopaths are often portrayed as having stereotypical preferences for classical music. We wondered whether this is an accurate representation of this condition and whether psychopaths differ from controls in terms of aesthetic preferences in general. To address this empirically, we assessed 193 individuals from the NYU undergraduate population in terms of their psychopathic traits, as measured by the Levenson Self-Report Psychopathy Scale (LSRP). We then queried their preference for 260 carefully selected musical stimuli, clips of songs determined to be characteristic of the entire song, from a diverse range of genres and sub-genres. Doing so, we identified a subset of songs that can be used to identify individuals with psychopathic traits. However, we could not substantiate that individuals with high psychopathic traits - as measured by the LSRP - exhibit a preference for classical music.

Disclosures: N.A. Leal: None. **P. Wallisch:** None.

Poster

089. Individual Differences

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 089.02/TT53

Topic: H.02. Human Cognition and Behavior

Title: Trait impulsiveness is related to smaller ventral putamen volumes in males but not females

Authors: *F. CARAVAGGIO[1], E. PLITMAN[2], J. K. CHUNG[2], P. GERRETSEN[2], J. KIM[2], Y. IWATA[2], M. CHAKRAVARTY[3], G. REMINGTON[2], A. GRAFF-GUERRERO[2]
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Abstract: Background: Impulsivity is considered a vulnerability trait for addiction. Recently, we found trait non-planning impulsivity measured with the Karolinska Scales of Personality (KSP) was negatively correlated with dopamine (DA) $D_{2/3}$ receptor ($D_{2/3}R$) availability in the ventral striatum (VS) of healthy humans. While also observed in rodents, human studies have failed to find this association with other measures of trait impulsivity. We explored whether another rodent finding, reduced VS volume with greater impulsivity, could also be observed in humans using the KSP. **Methods:** Non-planning impulsiveness was measured in 52 healthy subjects (21 female; mean age: 33.06±9.69) using the KSP. Striatal sub-region volumes, including the globus pallidus, were acquired using the Multiple Automatically Generated Templates (MAGeT-Brain) algorithm. We examined, in an overlapping sample, whether

findings with the KSP could be extended to another measure of non-planning impulsiveness, captured by the Temperament and Character Inventory (TCI) (n=73; 32 female; mean age: 33.48±9.75). **Results:** KSP-impulsiveness was negatively correlated with ventral putamen (VP) volumes in males (r^2=.40, *p*=.0003), but positively correlated in females (r^2=.22, *p*=.04). TCI-impulsiveness was negatively correlated with VP volumes in males (r^2=.14, *p*=.02), but not in females (r^2=.04, *p*=.33). The findings with the KSP in males survived correction for multiple comparisons. **Conclusions:** While increased impulsivity may be related to reduced VS $D_{2/3}R$ across sexes, males but not females may show significant reductions in VP volume. These findings have important implications for understanding biological markers underlying sex-differences in drug addiction vulnerability.

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Poster

089. Individual Differences

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 089.03/TT54

Topic: H.02. Human Cognition and Behavior

Title: The use of defined inclusion criteria to establish cognitive deficits in clinical trials of interventions on cognition performance

Authors: *J. L. EVENDEN[1], K. GRANGER[2]
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Abstract: Introduction: Cognitive deficits have been documented at the group level in CNS disorders such as schizophrenia, major depressive disorder, ADHD and Parkinson's disease, but the degree of individual impairment varies greatly. Not all patients fulfilling diagnostic criteria also have a clinically problematic level of cognitive function, below the normal range expected in the absence of the illness. If such patients are included in research studies of cognition in these conditions, the results may be misleading, and perhaps contribute to the lack of success of drug discovery and development in this area. Methods: Systematic searches were carried out on clinical trials.gov for protocols (Dec 2013 - Nov 2016) targeting five major CNS disorders associated with cognitive deficits: Schizophrenia (Schiz: n=368), Alzheimer's Disease (AD, n=299), Parkinson's Disease (PD, n=466), Major Depressive Disorder (MDD, n=296) and Attention Deficit Hyperactivity Disorder (ADHD, n=162). Information was collated on the study objectives, treatment intervention, cognitive endpoints and quantitative or qualitative inclusion/exclusion criteria. Results: In Schiz, of 154 studies including cognitive endpoints, only

6 employed inclusion criteria to establish the presence of a cognitive deficit (3.9%). In PD, 111 studies included cognitive endpoints, but only 13 established the presence of cognitive deficits (11.7%). Corresponding numbers for MDD were 2 of 58 (3.4%), and for ADHD, 15 of 80 studies (18.8%). In contrast, in AD, despite the implication of a cognitive deficit in the clinical diagnosis, 94 of 173 studies including cognitive endpoints also employed quantitative inclusion criteria (54.3%). However, 56 of 107 AD studies which did not assess cognition also used quantitative cognitive inclusion criteria (52.3%). Conclusion: Of studies using cognitive endpoints in Schiz, PD, MDD and ADHD, only a small minority employed formal inclusion criteria to establish a cognitive deficit. In contrast, quantitative inclusion criteria are widespread in AD research, although the frequent use when cognition assessments were not part of the study protocol suggests the purpose may often be to quantify disease severity. AD research shows that cognitive deficits can be routinely quantified at screening, primarily using a brief assessment (e.g. MMSE). Employing appropriate inclusion criteria would ensure that participants included in studies investigating cognition in neuropsychiatric disorders have been confirmed to have the deficit being investigated, and increase the likelihood that study results are truly relevant to this important clinical problem.

Disclosures: **J.L. Evenden:** A. Employment/Salary (full or part-time):; Cambridge Cognition. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); WiltonLogic. **K. Granger:** A. Employment/Salary (full or part-time):; Cambridge Cognition.

Poster

089. Individual Differences

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 089.04/TT55

Topic: H.02. Human Cognition and Behavior

Title: Relationship between autism spectrum disorder tendencies and selective inhibition of irrelevant information in sensory-motor response

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Abstract: One character of autism spectrum disorder (ASD) is persistent deficits in social interaction, and restricted, repetitive patterns of behavior, interests, or activities. The characters are related to the abilities of selection of task-relevant information and inhibition of task-irrelevant information. The abilities might be related to neural mechanisms of sensory-motor response, which includes the motor area and the posterior sensory areas (e.g. occipital areas for visual information processing and temporal areas for auditory information processing). The distant brain areas connect each other through a global network with phase synchronization in

recent human electroencephalography (EEG) studies. Although the alpha global synchronization between the motor and sensory areas play important roles in motor-response tasks, the relationship of the global synchronization with the ASD symptoms are not clear. To address the issue, the present study aim to clarify sensory-motor synchronizations with EEG experiments and analyses. All participants completed two types of simple motor-response tasks (a single auditory-motor response task (AM) and a single visual-motor response task (VM) for the single sensory information) and two types of selection-motor-response tasks (a auditory-selection-motor response task (ASM) and a single visual-selection-motor response task (VSM) for the dual sensory information). Behavioral results showed that the response time for ASM and VSM tasks was longer than that for the AM and VM tasks. Interestingly, the prolong times were positively correlated with the ASD symptoms. The time-frequency analyses for the EEG data showed that the alpha phases in the motor areas were functionally synchronized with those in the visual areas during the VM and VSM task but not the AM and ASM task. In contrast, the alpha phase synchronization between the motor and auditory areas were found in only the AM and ASM task but not the VM and VSM task. These task-relevant alpha phase synchronizations were decreased in the participants with high scores of the ASD symptoms. These results suggested that the ASD deficits would be associated with the decrements of the alpha synchronizations between the motor areas and the task-relevant sensory areas.

Disclosures: M. Kawasaki: None. **E. Miyauchi:** None.

Poster

089. Individual Differences

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Program#/Poster#: 089.05/TT56

Topic: H.02. Human Cognition and Behavior

Title: Brain state perturbation improves connectome-based predictive modeling of related behaviors

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Abstract: Recent advances in human neuroimaging techniques – in particular, functional connectivity (FC) analyses – are revealing robust individual differences in patterns of neural activity that predict behavioral measures and clinical symptoms (e.g., Finn et al., 2015). FC is usually calculated using data acquired during rest; without tasks to perturb neural circuitry, these data may fail to represent the full range of individual differences in FC (Finn et al., 2017). In this work, we demonstrate that, much like a cardiac stress test identifies symptoms not observable at

rest, tasks that tax individuals along a particular cognitive dimension amplify individual differences in the neural representations of that dimension and correspondingly improve prediction of related behaviors.
These analyses use fMRI data from the Human Connectome Project (HCP; n = 493); each subject performed 2 rest and 7 task runs in the scanner. These data were parcellated into 268 nodes (Shen et al., 2013), and the mean timecourses of each node pair were correlated, generating nine 268x268 connectivity matrices per subject. These matrices were each submitted to the connectome-based predictive modeling (CPM) pipeline (Shen et al., 2017) to generate cross-validated predictive models of fluid intelligence (gF). Model performance was quantified as the correlation between predicted and true gF. We repeated this analysis using fMRI data from the Philadelphia Neurodevelopmental Cohort (PNC; n = 571); each subject performed 1 rest and 2 task runs in the scanner, and data from all runs were submitted to the pipeline described above. Finally, to leverage independent information in task-based connectomes, we developed a multidimensional CPM approach that uses canonical correlation analysis to optimally combine data across tasks into a single connectivity matrix prior to model development.
In both datasets, tasks that tap into high-level cognitive functions yield better predictions of gF than do unrelated tasks or rest (HCP tasks, r = 0.26 – 0.39, all $p < 0.001$; HCP rest, r = 0.06 – 0.18, p = 0.20 and 4.6E-5, respectively; PNC tasks, r = 0.32 – 0.35, all $p < 0.001$; PNC rest, r = 0.20, $p < 0.05$). External validation demonstrates that these models generalize across tasks (r = 0.22 – 0.39, all $p < 0.001$) and across datasets (r = 0.08 – 0.21, all $p < 0.02$ [except when applying two PNC rest models to HCP rest, in which cases p = 0.07 and 0.04]). Multidimensional CPM further improves model performance (e.g., HCP r = 0.44, $p < 0.001$). These results suggest an opportunity to use task-based fMRI to more comprehensively characterize individual differences in FC and to relate these differences to meaningful variation in human behavior.

Disclosures: **A.S. Greene:** None. **S. Gao:** None. **R.T. Constable:** None. **D. Scheinost:** None.

Poster

089. Individual Differences

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Program#/Poster#: 089.06/TT57

Topic: H.02. Human Cognition and Behavior

Title: Dissecting the link between cortical brain morphology and human intelligence

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Abstract: Human intelligence (g) can be decomposed into two factors: fluid intelligence (gf) and crystallized intelligence (gc). While gc mostly captures verbal abilities, which are acquired

throughout the lifespan, gf is associated with abstract reasoning, which declines with age. Considering their different trajectories, gc and gf are likely associated with different cortical morphologies, such as cortical thickness, surface area and gyrification. Cortical surface area is associated with the number of cortical minicolumns, which enable higher parallel computational power. On the other hand, thickness is associated with dendritic arborizations and neuron densities, which change with learning and is more related to consolidated knowledge. Previous studies have focused on correlation between cortical thickness and intelligence, with inconsistent findings across studies. Here we identified predictors of g, gf and gc on a large dataset (human connectome project -HCP, n=740, age range=21-35) and validated results on an independent dataset based on different MRI and cognitive measures (INDI, n=250). Thickness, surface area and gyrification were measured at each vertex using Freesurfer. HCP subjects were split into 10 folds to get more robust clusters. For each fold, a linear regression model was fitted for g, gf and gc at each vertex while controlling for age, gender and total brain volume. Significant clusters were then tested on INDI to verify generalizability of findings. Results confirmed that distinct cortical morphologies are associated with gf and gc. Surface area in left/right superior parietal and left/right temporal gyri were positively correlated with gf (R2=15%), whereas left middle frontal and right inferior/middle temporal gyri were positively correlated with gc (R2=14.5%). On the other hand, thickness in left middle/inferior frontal gyrus showed negative correlation only with gc (R2=12.2%). As a less specific substrate for intelligence, gyrification in parietal and frontal lobes was positively correlated with both gf and gc (R2=12%). Our findings suggest that surface area and thickness might provide distinct cortical substrates for fluid and crystallized intelligence. Larger cortical surface area in parietal regions (gf) might enable resources to be dynamically reallocated during perceptual search, while decreased cortical thickness in language-related regions (gc) might be the result of an experience-dependent optimization aimed at increasing efficiency.

Disclosures: **S. Tadayon:** None. **A. Pascual-Leone:** None. **E. Santarnecchi:** None.

Poster

089. Individual Differences

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: UAB Nutrition Obesity Research Center Training Grant (T32HL105349)

Title: The critical role of cognitive-based trait differences in transcranial direct current stimulation suppression of food craving and eating in frank obesity

Authors: *M. RAY, M. D. SYLVESTER, L. OSBORN, J. HELMS, B. TURAN, M. M. BOGGIANO
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Abstract: Obesity remains a major public health concern and novel treatments are needed. Transcranial direct current stimulation (tDCS) is a neuromodulation technique shown to reduce food craving and consumption, especially when targeting the dorsolateral prefrontal cortex (DLPFC) with a right anode/left cathode electrode montage. Despite the implications to treat frank (non-binge-eating) obesity, no study has tested the right anode/left cathode montage in this population, nor controlled for differences in traits under DLPFC control that may influence how well one responds to tDCS. Hence, N=18 (10F/8M) adults with frank obesity completed the Dutch Eating Behavior Questionnaire-Restraint and Barratt Impulsiveness Scale, and received 20 minutes of 2mA active tDCS and control tDCS session. Craving and eating was assessed at both sessions with a food photo "wanting" test and in-lab measures of total, preferred, and less-preferred kilocalories consumed of three highly palatable snack foods. While main effects of tDCS vs. control were not found, significant differences emerged when trait scores were controlled. tDCS reduced food craving in females with lower attention-type impulsiveness ($p=0.047$), reduced preferred-food consumption in males with lower intent to restrict calories ($p=0.024$), and reduced total food consumption in males with higher non-planning-type impulsiveness ($p=0.009$) compared to control tDCS. This is the first study to find significant reductions in food craving and consumption in a sample with frank obesity with the most popular tDCS montage used in appetite studies. The results also highlight the cognitive-based heterogeneity of individuals with obesity and the importance of considering these differences when evaluating the efficacy of tDCS in future studies aimed at treating obesity.

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Poster

089. Individual Differences

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Program#/Poster#: 089.08/TT59

Topic: H.02. Human Cognition and Behavior

Support: Toyota Motor Corporation

RIKEN Research Funds for Data Assimilation

Title: EEG metastable states and individual differences for the resting human brain

Authors: *T. SASE, K. KITAJO
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Abstract: Previous studies have shown that the dynamics generating electroencephalography (EEG) signals spontaneously transitions among four states under a resting condition. These states have been called the EEG microstates and suggested to be reflecting individuality for humans as well as disease states for patients. Thus, it has been expected that the microstate analysis is the key to understanding brain functions such as cognition, but interpreting EEG microstates from the underlying mathematical aspects, particularly dynamical systems theory, remains unclear. In fact, the microstate analysis implicitly assumes that EEG dynamics yields a trajectory moving among fixed points from the dynamical systems viewpoint, because each microstate is a map obtained from a clustering method. However, EEG signals exhibit clear oscillations evidencing that the underlying attractor is the torus with dimension larger than zero.
To overcome this issue, we extend the definition of EEG microstates so that the actual EEG metastable states are included in the clustered states, calling a set of these states as mesostate x assuming that the dimension of tori generating EEG dynamics is x, and develop a new clustering method that can distinguish EEG signals into metastable states. This procedure would lead to interpreting EEG microstates from metastable states.
To reveal EEG metastable dynamics, we recorded 63-channel scalp EEG signals during 180 s in an eyes-closed resting condition from 80 healthy humans. We applied the mesostate analysis, which utilizes dimensionality reduction of tori using multi-step envelope analysis and that of space using the linear discriminant analysis, to the signals under the two assumptions: (i) 63 dimensions are sufficient to describe the EEG dynamical system; and (ii) multistable states underlie its dynamics. The results showed that EEG dynamics spontaneously transitions among mesostate 2 generating phase-amplitude coupling, where the instantaneous amplitude around 10 Hz was modulated by the instantaneous phase around 1 Hz. Further, we found evidence that the number of metastable states depends on individuals, where the number of clusters was chosen based on the Fisher criterion assuming that brain functions represented by each state are largely different, i.e., distance between states is sufficiently large.
Moreover, to elucidate the mechanism behind EEG metastable states and to clarify metastability-specific individual differences, we performed EEG-data assimilation using the Kuramoto model and estimated the underlying connectivity. We conclude here that metastability and individuality may originate from connectivity on phase dynamics.

Disclosures: T. Sase: None. **K. Kitajo:** None.

Poster

089. Individual Differences

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Program#/Poster#: 089.09/TT60

Topic: H.02. Human Cognition and Behavior

Support: ARL #W911NF-10-2-0022

Title: Using data-driven models of brain network dynamics to predict individual performance in cognitively demanding tasks

Authors: K. BANSAL[1], J. D. MEDAGLIA[2], D. S. BASSETT[2], J. M. VETTEL[3,2,4], *S. E. MULDOON[5]
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Abstract: Humans show individual differences in cognitive performance, and the origin of this variability is not completely understood. How important is the anatomical wiring of the brain in explaining and predicting individual differences in cognition? Here, we use a data-driven computational network model that combines structural connectivity with nonlinear Wilson-Cowan oscillators to study the spatiotemporal dynamics of a human brain. We estimate anatomical white matter connections from diffusion spectrum imaging in a cohort of ten healthy adult individuals. These same participants also performed three language-related tasks - verb generation, sentence completion, and number reading. Task performances were measured before and after transcranial magnetic stimulation to the left inferior frontal gyrus (L-IFG). Motivated by experimental data, we perform computational experiments in which we stimulate L-IFG in our model and quantify the spread of the stimulation both within the global brain network, and throughout the task specific sub-networks across subjects. We then relate the patterns of activation to individual performance across three tasks and find that task performance correlates with the activation of either local or global circuitry depending on the complexity of the task. By emphasizing differences in the underlying structural connectivity, our model serves as a powerful tool to predict individual differences in task performances and to discern the effect of targeted stimulation on tasks of differing cognitive complexity.

Disclosures: K. Bansal: None. **J.D. Medaglia:** None. **D.S. Bassett:** None. **J.M. Vettel:** None. **S.E. Muldoon:** None.

Poster

089. Individual Differences

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Some data contributed by HCP (NIH 1U54MH091657)

Title: Head displacement has predictable temporally extended effects on the BOLD signal that persist after preprocessing and influence functional connectivity estimates

Authors: *L. BYRGE, D. P. KENNEDY
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Abstract: Head motion is problematic for the BOLD signal – particularly for techniques such as functional connectivity MRI (fcMRI), where findings can be spuriously influenced by movement differences. Yet current preprocessing practices might not fully eliminate residual motion influences. Here we present a new method for assessing residual movement-linked BOLD artifact, by quantifying the relationship between movement severity and subsequent BOLD activity. We analyzed resting-state fMRI scans from Indiana University (2-6 16min scans, TR=813ms, *N*=53) and the Human Connectome Project (2 14min scans, TR=720ms, *N*=75). Datasets were preprocessed a number of different ways including ICA-FIX, conventional GLM preprocessing, and minimal preprocessing. We found that movements were systematically linked with structured and prolonged changes in the BOLD signal that depend on the severity of the preceding motion. Nearly all motions (including remarkably small movements below typical censoring thresholds) were associated with structured BOLD changes extending 25-30 TRs later. Effect sizes of motion-linked BOLD changes were largest approximately 5 TRs and 20 TRs following motion. These patterns were replicated across different sessions, scanners, and preprocessing methods (but not observed in four different null models) and explain a considerable range of variance (up to 45%) in the global BOLD signal. These lagged motion-BOLD interactions are not yet accounted for by most state-of-the-art preprocessing methods, and they persist much later than typical censoring/“scrubbing” procedures can address. They have a serious consequence: functional connectivity estimates, even after the strictest censoring (FD > .2 mm), vary as a function of motions occurring up to 30 TRs in the past. Although global signal regression remains a controversial preprocessing step, we find that it attenuates these residual motion effects and minimizes the associated alterations in functional connectivity. Our results thus support the use of global signal regression, and more broadly, suggest caution in interpreting different patterns of functional connectivity between individuals or groups whose head motion differs, until these interactions between motion and BOLD are more fully understood and addressed.

Disclosures: L. Byrge: None. **D.P. Kennedy:** None.

Poster

089. Individual Differences

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Topic: H.02. Human Cognition and Behavior

Support: ImPACT

SRPBS from AMED

Title: The site bias estimated from traveling-subject-data can improve a resting-state connectivity-based prediction model

Authors: *A. YAMASHITA[1], T. YAMADA[2], N. ICHIKAWA[4], M. TAKAMURA[4], Y. YOSHIHARA[5], T. ITAHASHI[6], G. OKADA[4], H. MANO[7,3], Y. SAKAI[8,3], J. MORIMOTO[2], N. YAHATA[9,10,3], R. HASHIMOTO[6,3], H. TAKAHASHI[5], Y. OKAMOTO[4], M. KAWATO[2], H. IMAMIZU[11,1]
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Abstract: Recently, there are an increasing number of multi-site resting-state functional MRI connectivity studies. Resting-state functional connectivity (rs-FC) has been used to make neuroimaging-based prediction models, such as a classifier for psychiatric disorders and a regression model to predict subject's age. While multi-site study allows investigators to increase sample size, this also introduces systematic biases in connectivity measures. Although a previous study shows that systematic site bias is sufficiently smaller than the effect of subject but another study shows that the site bias has a significant impact on prediction accuracy of the models. Thus, methods for reducing systematic site bias are needed. Typically, site biases are estimated and subtracted from connectivity measures by using a linear regression. This method has, however, the problem that the estimated site biases include unique features that characterize distinct subjects, since subjects are inevitably different among sites. In this study, we estimated pure site biases dissociated from contamination effects of subjects by using traveling-subject rs-FC data (nine subjects travelled to 9 sites and were scanned at each site). As cases testing effectiveness of the traveling-subjects, we created two prediction models by using another multi-site rs-FC data of 643 subjects including depressed patients obtained from the same sites as traveling-subject rs-FC data (depressed patients: n = 161, 75 males; mean age, 42.6 ± 11.6

(1SD); age range 21-73, healthy: n = 482, 209 males; mean age, 30.5 ± 10.9; age range 18-68). The two prediction models are 1) a classifier for major depressive disorder, and 2) a regression model to predict subject's age. We then investigated whether we can improve a multi-site rs-FC based prediction model by subtracting the pure site bias from rs-FC. As a reference, we also made two prediction models based on rs-FC denoised by subtracting the site bias estimated using conventional regression method. Overall, by subtracting the pure site bias, area under the curve was improved by 0.13 (from 0.60 to 0.73), accuracy and specificity were improved by 12% (from 55% to 67%), and sensitivity was improved by 10% (from 56% to 66%) in a classifier and root mean squared error was reduced by 0.1 (from 10.16 to 10.05) in a regression model in comparison to the conventional regression method. This result shows that traveling subject data provides the pure site bias and that we can improve a multi-site rs-FC based prediction model by subtracting the pure site bias from rs-FC.

Disclosures: **A. Yamashita:** None. **T. Yamada:** None. **N. Ichikawa:** None. **M. Takamura:** None. **Y. Yoshihara:** None. **T. Itahashi:** None. **G. Okada:** None. **H. Mano:** None. **Y. Sakai:** None. **J. Morimoto:** None. **N. Yahata:** None. **R. Hashimoto:** None. **H. Takahashi:** None. **Y. Okamoto:** None. **M. Kawato:** None. **H. Imamizu:** None.

Poster

089. Individual Differences

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Topic: H.02. Human Cognition and Behavior

Support: ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan)

The New Energy and Industrial Technology Development Organization(NEDO)

CREST, JST

Title: Large-scale network associated with creative insight: Data-driven approach by using VBM-constrained resting-state functional connectivity analysis

Authors: *T. OGAWA[1], T. AIHARA[2], T. SHIMOKAWA[2], O. YAMASHITA[2]
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Abstract: Creative insight occurs with "Aha!" experience in solving a difficult problem. Here, we focused on large-scale network associated with insight problem solving. We conducted an MRI experiment (structural image and 10-min resting-state fMRI scanning) and an insight test battery (ITB) which consisted of written questionnaires (matchstick arithmetic, remote associates test and insight problem) on 162 healthy participants and aged from twenties to sixties. To

identify resting state functional connectivity (RSFC) associated with individual creative insight, we conducted voxel-based morphometry (VBM) constrained RSFC analysis with data-driven approach.We identified two clusters in the right posterior insula cortex (pIC) and right posterior middle cingulate cortex (pMCC) where the gray matter volumes were positively correlated with the ITB score. We applied seed-based RSFC analysis to whole brain voxels by using seeds, pIC and pMCC, obtained from VBM, and then found insight-positive/negative connections, that is positive/negative correlation between the ITB score and strengths of RSFC between two brain regions. We identified insight-positive connections from right pIC as a seed to regions associated with left inferior parietal lobule in default mode network (DMN) and right dorsolateral prefrontal cortex (DLPFC) in executive control network (ECN). We also found insight-negative connections from right pIC to visual processing regions (left inferior temporal gyrus: ITG, right fusiform gyrus). From another seed, the right pMCC, we found insight-positive connection to right middle temporal gyri (MTG) which are associated with semantic language process. Our results indicate that pIC plays a role of switching DMN and ECN, and dissociation between right pIC and visual processing region are important for idea-evaluation to achieve higher creative insight. About pMCC, association between DMN and semantic language process may support memory retrieval, then it may help to perform higher creative insight.

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Poster

089. Individual Differences

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Program#/Poster#: 089.13/TT64

Topic: H.02. Human Cognition and Behavior

Support: SRPBS from AMED

Title: Functional connectivity MRI biomarkers may serve as biological dimensions of multiple psychiatric disorders

Authors: G. LISI[1], Y. YOSHIHARA[3], N. YAHATA[4], R. HASHIMOTO[5], T. YAMADA[2], K. KASAI[6], N. KATO[7], H. TAKAHASHI[3], J. MORIMOTO[1], *M. KAWATO[8]
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Abstract: The Research Domain Criteria (RDoC) project aims to be complementary to the Diagnostic and Statistical Manual of Mental Disorders (DSM), by redefining boundaries among

psychiatric disorders. One of their most influential works is the study by Clementz et al. 2015, where unsupervised machine learning was used to discover biomarkers that outperform DSM in parsing psychosis subgroups, based on a relatively low dimensional set of brain-related biomarker variables. However, we find three limitations in such RDoC approach. First, similar biomarkers, based on high dimensional whole-brain imaging data, would suffer from the curse of dimensionality. Second, unsupervised learning requires a vast amount of data, which is expensive. Third, the conclusions of RDoC studies risk to be contradictory, rather than complementary to DSM.
Here we propose a novel approach that combines DSM and RDoC in order to overcome their respective drawbacks. DSM-based functional connectivity MRI biomarkers, that generalize to independent cohorts, were designed for several psychiatric disorders: autism spectrum disorder (ASD, Yahata et al. 2016, *Nature Communications*), major depressive disorder (Ichikawa et al. 2017, *arXiv:1704.01039*), obsessive compulsive disorder (Takagi et al. 2017, *arXiv:1703.05428*), schizophrenia spectrum disorder (SSD, in preparation). The resulting probabilistic classifiers, not only classify patients from controls, but provide a degree of classification certainty, which can be interpreted as neural liability to a specific disorder. Therefore, the neural liability scores provided by each classifier represent new biological dimensions that can be used to redefine multiple psychiatric disorders using the RDoC framework.
We applied this novel approach to ASD and SSD and found that the neural liability scores defined by the two classifiers correlate significantly in ASD patients, but not in SSD patients. Furthermore, as reported in Yahata et al. 2016, SSD patients can be distinguished from controls using the ASD classifier. However, we found that the same cannot be done for ASD patients using the SSD classifier. These findings suggest an intimate but asymmetrical relationship between ASD and SSD, that requires further investigation.

Disclosures: **G. Lisi:** None. **Y. Yoshihara:** None. **N. Yahata:** None. **R. Hashimoto:** None. **T. Yamada:** None. **K. Kasai:** None. **N. Kato:** None. **H. Takahashi:** None. **J. Morimoto:** None. **M. Kawato:** None.

Poster

089. Individual Differences

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 089.14/TT65

Topic: H.02. Human Cognition and Behavior

Support: SRPBS from AMED

MEXT

NINDS grant R01NS088628

Title: Within-participant bidirectional confidence changes induced by multivoxel patterns manipulation

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Abstract: A central controversy in current studies of metacognition concerns whether confidence directly reflects the reliability of a perceptual process. This normative view enjoys popularity in both the computational and animal literatures, but several studies also suggest that the computation of confidence may depend on late-stage estimation processes dissociable from actual reliability. Nevertheless, particularly in humans, experimental approaches have lacked the resolution to convincingly resolve these issues. Recent advances in real-time functional magnetic resonance imaging (rtfMRI), including the ability to perform complex multivariate decoding analyses online, have opened new possibilities to overcome this challenge. We employed the recently-developed method of decoded neurofeedback (DecNef) to systematically manipulate multivoxel correlates of confidence in a frontoparietal network. In a counterbalanced within-subjects' design, participants learned to implicitly induce either high or low confidence activation patterns in two separate sessions. Our results provide explicit evidence that confidence can be dissociated from perceptual performance; we selectively manipulated the former without changing the latter. Further psychophysical analysis ruled out accounts based on simple shifts in criterion or reporting strategy for confidence. Since the confidence changes were strongly influenced by the order and the directionality of neurofeedback training, we applied nonlinear mathematical modeling to parametrize the main consequences of DecNef. Modeling results provide additional evidence that DecNef successfully induced bidirectional confidence changes within single participants. Furthermore, the effect of up- compared to down-regulation was more prominent, and confidence changes were largely preserved even after a week-long interval. Lastly, a largely diminished DecNef effect in the second session as compared with the first indicated strong anterograde learning interference. Taken together, these findings challenge the current dominant views of confidence and metacognition. Because of the great potential for clinical applications, these results are also taken to elucidate critical aspects regarding DecNef. Specifically, single participants can learn to induce neural patterns in opposite directions in different sessions, but previous learning strongly affects subsequent induction effectiveness, thus potentially requiring longer training designs. These results also provide important implications for neurofeedback applications to basic neuroscience, occupational and sports training, and to therapy.

Disclosures: A. Cortese: None. **K. Amano:** None. **A. Koizumi:** None. **H. Lau:** None. **M. Kawato:** None.

Poster

089. Individual Differences

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 089.15/TT66

Topic: H.02. Human Cognition and Behavior

Support: MEXT Development of BMI Technologies for Clinical Application

Title: A stably appeared latent neural representation across states is predictive of intelligence

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Abstract: Intelligence is a key factor in individual differences that is related to various aspects of our personal life, including school achievement, job success and longevity. Accumulating evidence suggests that there exists a core of intelligence that is correlated positively with various intelligence sub-tests, often termed 'general intelligence factor (g-factor)'. However, neural processes underlying g-factor still remains an open question. Here, based on recent data-driven, large-scale neuroimaging studies, we newly hypothesize that a stable trait in the brain's functional connectivity, largely unaffected by different task states, is the neural source of g-factor; we refer to this notion as `common neural mode (CNM).' In the present study, we identified an NGF with the functional magnetic resonance imaging data of more than 400 subjects, measured during both rest and seven distinct tasks. Then we examined how the CNM correlates with behavioral measures that are known to reflect g-factor, among hundreds of others. Finally, we investigated whether the CNM improves the prediction of individual's life achievements. As the result, we found that among hundreds of behavioral measures, fluid intelligence has the strongest correlation with CNM, which is thought of as a fundamental component of general intelligence. The correlation between CNM and intelligence measures was not restricted both in the cognitively demanding task states and in resting state. Furthermore, we also found that combining CNM with conventional intelligence measures predicts better the individual's life achievements than using only the conventional measures.

Disclosures: Y. Takagi: None. **J. Hirayama:** None. **S.C. Tanaka:** None.

Poster

089. Individual Differences

Location: Halls A-C

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Program#/Poster#: 089.16/UU1

Topic: H.02. Human Cognition and Behavior

Title: Ethnic differences in spatial ability: The influence of environment and culture

Authors: *L. YUAN, S. WAN, M. MA, X. ZHOU
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Abstract: Abstract: Studies in the past argued that the differences in spatial ability were impacted by biological, environmental factors and culture. The current study aimed at exploring ethnic differences in spatial ability among the students in Han, Uygur, Mongolian and other ethnic minority areas. The students were from 13 primary and secondary schools (n=2338, 477 Han, 765 Uygur, 546 Mongolian, 550 other ethnic minorities). They completed six tasks including mental rotation, choice reaction time, raven reasoning, sound perception, figure matching and dot comparison. The results showed that there were significant differences in all these tasks among four nation groups. Moreover, we found that the spatial ability of the Mongolians was significantly better than that of other nationalities, even after controlling all the other general cognitive factors. It suggested that spatial abilities may be influenced by interaction from environment and culture.

Disclosures: L. Yuan: None. **S. Wan:** None. **M. Ma:** None. **X. Zhou:** None.

Poster

089. Individual Differences

Location: Halls A-C

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Program#/Poster#: 089.17/UU2

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant HD69162

Title: Characterizing white matter tracts in 8-year-old children born preterm and full term using diffusion and quantitative magnetic resonance imaging

Authors: *M. R. CASTRO[1], K. E. TRAVIS[3], S. BERMAN[4], A. MEZER[5], M. BEN-SHACHAR[6], H. M. FELDMAN[2]
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Abstract: ***Intro:*** Children born < 33 weeks gestation may experience diffuse white matter injury from complications of preterm (PT) birth. Previous studies using Diffusion Tensor Imaging (DTI) found differences in fractional anisotropy (FA) between children and adolescents born PT and full term (FT), suggesting persistent changes in white matter structure. PT was associated with reduced FA in some tracts and elevated FA in other tracts. To determine if these FA differences between birth groups represent differences in myelin content, we collected DTI and fast, high-resolution quantitative R1 (qR1). R1 (1/T1), the MRI longitudinal relaxation rate, was found to be a good index of myelin content.
Methods: We obtained DTI and qR1 3T data in 21FT and 22PT children age 8y. qR1 scans were acquired using a spoiled gradient echo sequence (flip angles 4°, 10°, 20°, 30°) corrected for inhomogeneity with an EPI readout spin echo inversion recovery sequence with multiple inversion times (TI = 400, 1200, 2400ms). Whole-brain deterministic tractography and automated tract quantification were used to segment, bilaterally, the inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and Forceps Major (FMajor). To minimize the number of group comparisons, we divided each tract into two segments and calculated mean FA and mean R1 for each segment. We performed separate one-way multivariate analysis of variance (MANOVA) for each tract segment to assess whether PT and FT demonstrated differences in FA or R1.
Results: Compared to FA in the FT group, FA in the PT group was significantly higher in the anterior half of SLF-R ($F=15.55$, $p<0.001$), the posterior half of ILF-L ($F=9.65$, $p<0.005$) and the posterior half of ILF-R ($F=6.87$, $p<0.05$). Compared to the FT group, R1 in the PT group was significantly higher in the anterior half of the ILF-L ($F=5.58$, $p<0.05$) and significantly lower in the FMajor-R ($F=4.25$, $p<0.05$).
Conclusions: The DTI results replicate prior findings from PT and FT children at age 6y and 9-17y. Only a subset of these findings can be explained by differences in myelin content, as indexed by R1. R1 elevation in the ILF-L of PT suggests increased myelin content in PT in this tract. R1 reduction in PT in the FMajor-R suggests lower myelin content in PT in this tract. These findings suggest that birth group differences in FA are likely driven by multiple factors, including, but not limited to, myelin. Directional coherence is likely to be the main driving force behind the FA differences detected in the SLF and ILF-R.

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Poster

089. Individual Differences

Location: Halls A-C

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Program#/Poster#: 089.18/UU3

Topic: H.02. Human Cognition and Behavior

Title: Beyond the big 5: Enjoyment of horror movies, personality and sensation seeking

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Abstract: We are interested in whether we can predict who will like horror movies. Prior research, e.g. Steinberg et al. (2012) suggest that it should probably be people low in introversion and neuroticism. Here, we asked 800 participants about their appraisal of 400 movies, including 40 horror movies. We also established their big-5 profile and asked about risk-taking and sensation seeking behavior in general. Using this high powered sample, we can show that none of the personality dimensions predicts liking of horror movies. In addition, other risk-taking or sensation seeking behavior such as a predilection for rock climbing, bungee jumping or driving fast does not predict appraisal of horror movies either. Only an appreciation for closely related experiences (e.g. liking haunting houses) allowed to substantially predict the appraisal of horror movies. This research suggests the existence of an emotional - in addition to the socially defined - personality and that personality is "jagged", i.e. not easily described with a few parameters.

Disclosures: A.D. Trakhtorchuk: None. **P. Wallisch:** None.

Poster

089. Individual Differences

Location: Halls A-C

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Program#/Poster#: 089.19/UU4

Topic: H.02. Human Cognition and Behavior

Support: Student Blugold Commitment Differential Tuition

TRIO Ronald E McNair Postbaccalaureate Achievement Program

Title: Clinical perfectionism and electrophysiology of error processing: Associations with depression, anxiety, and fear of failure

Authors: A. M. YONKER, S. J. BECKER, S. M. MOE, L. J. BRANDT, S. T. LOEW, R. J. LOCKINGTON, K. A. ROLEFSON, *D. S. LELAND
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Abstract: The Clinical Perfectionism Questionnaire (CPQ; Shafran et al., 2002) is designed for the diagnosis and treatment of clinical perfectionism, which entails maladaptively critical self-evaluation based on excessively high standards. Previously, non-clinical measures of perfectionism have been shown to correlate with anxiety, depression, and fear of failure. Likewise, non-clinical perfectionism and clinical traits such as anxiety are associated with increased electroencephalographic (EEG) responses to self-committed errors. College students (n = 338, age = 18-26) completed an online survey including the CPQ and measures of anxiety (GAD-7), depression (CESD-R), and fear of failure (PFAI). All four measures were significantly and positively correlated with each other, and a multiple regression analysis showed CPQ was predicted by the other measures. Twelve survey respondents (so far) subsequently performed a flanker task (indicate the direction of a central curly brace in a series of five curly braces) during EEG recording to assess whether the error-related negativity (ERN), error positivity (Pe), or both are associated with the four survey measures. Results thus far replicate classic findings for both the ERN and Pe (both larger following incorrect than correct behavioral responses) and show a positive correlation between Pe and both anxiety (at site Pz) and depression (at site Fz, considering an apparent inversion in polarity of Pe at frontal sites). These findings demonstrate convergent validity for the CPQ and are beginning to reveal the relationship between clinical perfectionism and the neurocognitive processing of errors.

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Poster

089. Individual Differences

Location: Halls A-C

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Program#/Poster#: 089.20/UU5

Topic: H.02. Human Cognition and Behavior

Support: CPHS# 2010-01-567

Title: Taq1A genotype predicts dopamine's effects on amygdala-PFC functional connectivity

Authors: *J. R. NASKOLNAKORN, D. J. FURMAN, R. L. WHITE, M. D'ESPOSITO
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Abstract: Research in animal models has suggested that dopaminergic innervation of the basolateral amygdala mediates certain amygdaloid connections. In particular, dopamine can

modulate the inhibitory or excitatory effects of the bidirectional connections of the prefrontal cortex (PFC) and amygdala. While dopamine's effects on amygdala-PFC connectivity are implicated in a range of cognitive and emotional control processes, few human studies have investigated these effects directly. Motivated by findings in the animal literature, we used pharmacologic fMRI to assess changes in functional connectivity between the amygdala and PFC after the administration of bromocriptine, a dopamine D2 receptor (DRD2) agonist in human subjects. Given that our previous work has demonstrated that the response to dopaminergic agonists are dependent on endogenous dopamine system function, subjects were separated into groups based on their genotype for the DRD2-associated gene, Taq1A. The Taq1A polymorphism has been shown to have a strong association with striatal D2 binding potential. Importantly, Taq1A A1 carrier status is linked to significant decreases in D2 binding potential when compared to those with the A2 genotype.
Resting-state fMRI using Siemens 3T Trio scanner was performed in a cohort of healthy adults (ages 18-30) after administration of either bromocriptine (1.25mg) or placebo on two separate days. Saliva samples were collected during a prequalifying session and genotyping of the Taq1A polymorphism was conducted with PCR using TaqMan technology (Applied Biosystems). Functional connectivity analyses were performed on preprocessed data using subject-specific amygdala parcellations as seed regions.
We found a significant interaction between DRD2-Taq1A genotype and the effect of drug on functional connectivity between the amygdala and the right anterior PFC. Specifically, Taq1A A1 displayed a reduction in functional connectivity between the amygdala and anterior PFC following bromocriptine administration. Inversely, Taq1A A2 carriers exhibited increased connectivity in this amygdala-PFC network following bromocriptine administration. These findings are consistent with previous research where dopaminergic agonists were observed to cause inverted U-shaped effects on brain function. Further, our results support the hypothesis that dopamine can mediate functional connectivity between the amygdala and PFC.

Disclosures: J.R. Naskolnakorn: None. **D.J. Furman:** None. **R.L. White:** None. **M. D'Esposito:** None.

Poster

089. Individual Differences

Location: Halls A-C

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Title: An expanded set of regions of interest for functional network analysis: Improved representation of the subcortex and cerebellum

Authors: *B. A. SEITZMAN[1], C. GRATTON[1], B. L. SCHLAGGAR[1,2,3,4,5], S. E. PETERSEN[1,6,2,5], D. J. GREENE[4,2]
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Abstract: An important aspect of all network-based analyses is robust node definition. This issue is critical for functional brain network analyses in particular, as poor node choice can lead to spurious findings and misleading inferences about functional brain organization. Two sets of nodes from our group are well represented in the literature: (1) 264 volumetric regions of interest (ROIs) reported in Power et al. (2011), created via combined task fMRI meta analysis and resting-state functional correlation mapping, and (2) 333 surface ROIs reported in Gordon et al. (2016), created via data driven parcellation techniques.
These two sets of ROIs sample the cortex well, representing a diverse set of brain areas and systems. They have been used effectively to describe functional brain organization in healthy adult samples, developmental cohorts, and a variety of neurological and psychiatric disease populations by a wide range of investigators. However, important subcortical and cerebellar structures are either incompletely captured or missing from these ROI sets. Therefore, properties of functional network organization involving the subcortex and cerebellum may be underappreciated thus far.
Here, we apply winner-take-all parcellation and information-theoretic community detection techniques to resting-state fMRI data to generate novel ROIs in the thalamus, striatum, amygdala, hippocampus, and cerebellum. We validate the new ROIs in large groups of subjects via several anatomical and functional criteria, including known anatomical divisions and functions, as well as agreement with existing literature. Further, we demonstrate that the new subcortical and cerebellar ROIs combine with established cortical ROIs to recapitulate and extend previously described functional network organization. Finally, our new set of ROIs is made publically available for general use, including a full list of MNI coordinates and consensus functional network labels.

Disclosures: **B.A. Seitzman:** None. **C. Gratton:** None. **B.L. Schlaggar:** None. **S.E. Petersen:** None. **D.J. Greene:** None.

Poster

089. Individual Differences

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 089.22/UU7

Topic: H.02. Human Cognition and Behavior

Title: Oscillatory correlates of drug-induced cognitive impairment

Authors: *C. BARKLEY[1], Z. HU[2], M. DING[3], S. E. MARINO[4]
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Abstract: Many frequently prescribed drugs cause cognitive impairments in a subset of patients. As patients with epilepsy are particularly vulnerable to these side effects, there has been interest in cognitive deficits caused by anti-seizure drugs (ASDs) and the factors that make some individuals susceptible to experiencing adverse cognitive events. Topiramate (TPM) is a prime example of an ASD that causes severe impairments across a range of cognitive domains. With the aim of understanding the neural underpinnings of the pronounced variability in responses to TPM, we designed a double-blind, randomized, placebo-controlled study comparing TPM to placebo (PBO). On each visit, after receiving TPM or PBO, EEG was recorded while healthy participants performed a verbal working memory task previously shown to be highly sensitive to TPM. In order to identify brain responses to the encoding stimulus that co-varied with behavioral outcomes, we used data from both PBO and TPM sessions to calculate spectral power in the theta (frontal; 4-8 Hz), alpha (posterior; 8-13 Hz), and gamma (central; 30-80 Hz) frequency bands. Consistent with the literature, TPM administration led to pronounced performance deficits. In the absence of TPM, successful task performance was positively correlated with power in the gamma band, negatively correlated with alpha power, and characterized by long-distance cross-frequency alpha-gamma coupling. Intriguingly, gamma power observed during the PBO session was significantly correlated with the degree of TPM-induced impairment: subjects with high gamma power were particularly susceptible to the drug's negative impact, reflected in significantly more severe performance decrements after TPM administration. This relationship did not hold in the alpha or theta bands. These results suggest that, though high gamma power confers an advantage when performing the task under normal conditions, this pattern of brain activity appears to make an individual especially susceptible to TPM-induced cognitive impairment. In sum, these results suggest that gamma power may serve as a useful biomarker that can aid clinicians in identifying patients who may be vulnerable to TPM-induced cognitive impairments, enabling them to tailor treatment regimens accordingly.

Disclosures: C. Barkley: None. **Z. Hu:** None. **M. Ding:** None. **S.E. Marino:** None.

Poster

089. Individual Differences

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Topic: H.02. Human Cognition and Behavior

Support: National Research Foundation of Korea (NRF-2016R1C1B2016039)

KAIST (Future Systems Healthcare Project)

Title: Switching frequency of bistable perception reveals temporal integration of sensory information

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Abstract: When an ambiguous sensory stimulus (e.g., a Necker cube) is introduced, the perception of the stimulus often spontaneously switches between two distinct interpretations. This phenomenon, known as bistable perception, provides rich evidence pertaining to how the brain perceives ambiguous information. It has been considered that the perceptual switching of bistable perception is often periodic within the individual, but the switching frequencies vary across individuals (Kleinschmidt et al., 2012). How does perceptual switching occur quasi-periodically and why do individuals have different frequencies? In this study, we propose that each individual has an optimized temporal kernel which integrates the sensory information, and the size of kernel determines the subject's own switching frequency of bistable perception.
To examine our hypothesis, we performed a human psychophysics experiment using rotating dots in an annulus form (Jain, 2009). At each frame, a certain fraction *c* of the dots is rotating, and we controlled the parameter *c* to vary the ambiguity of the stimulus. When the rotational direction and *c* vary over time, the stimulus induces a noisy rotational motion, and the subjects' responses follow the given motion. In this case, we can measure the average stimulus pattern which triggers the perceptual switch by means of a reverse correlation method. On the other hand, when the stimulus does not have any coherent motion (c=0), the participants perceive bistable illusory motion and the perception alternates between the CW and CCW. In the latter case, we measured the time duration, i.e., the phase duration, of each perception.
The reverse correlation approach reveals that the average motion direction prior to the perceptual switch is identical to the altered perception. Earlier than that, the motion fades away and the direction reverses. This suggests that the brain detects the change of motion and that the perceptual alternation is determined by the temporal integration of motion. Moreover, the time window and the amplitude of the optimized stimulus showed a positive correlation with the phase duration. In addition, we observed that the response delay was positively correlated with

the phase duration, whereas the motion detection accuracy was not. This correlated behavior can also be
readily explained by the individual motion processing kernel.
In conclusion, we showed that the individual phase duration of bistable perception may emerge from optimal information integration and that perceptual behavior is highly dependent on the temporal dynamics of bistable perception.

Disclosures: W. Choi: None. **S. Paik:** None.

Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: AHA Grant 15CSA24460004

NSTRF14 Grant NNX14AL71H

DARPA Grant HR0011-17-C-0026

Title: Carbon nanotube based flexible and transparent neural electrode arrays

Authors: *J. S. YAN[1], F. VITALE[6], D. G. VERCOSA[2], K. N. BADHIWALA[1], R. HEADRICK[3], J. T. ROBINSON[4], M. PASQUALI[5]
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Abstract: Integrated optical and electrical modalities can unveil neural circuit dynamics that are crucial for understanding and treating neurological diseases. For example, simultaneous imaging and electrical recordings allow neural activity mapping at high spatial and temporal resolution, while optogenetics combined with electrophysiology allows concurrent probing and recording of neurons. Traditional metal electrodes are inadequate for these integrated, multimodal approaches due to their opacity. Recent works have proposed indium tin oxide (ITO) [1] and graphene [2, 3] as alternatives to metals for transparent multimodal interfaces. However, ITO electrodes are ill-suited for in vivo applications due to their brittleness and inability to conform to the convoluted surface of the brain. Graphene electrodes possess adequate flexibility to conform to the brain surface; while several groups have successfully demonstrated the use of graphene electrodes for simultaneous electrical recording, imaging and optogenetics [2, 3], to date the impedance of graphene electrodes cannot match that of metals without chemical doping, whose long-term stability and toxicity is yet to be demonstrated. Here, we present an alternative flexible and

transparent microelectrode arrays based on carbon nanotubes (CNTs). High performance isotropic CNT films are fabricated from solution-processing of pristine CNTs using vacuum filtration method. CNT films are patterned using standard microfabrication techniques, such as photolithography and reactive ion etching, and encapsulated in parylene passivation layers. Resulting electrode arrays are flexible and transparent: the sheet resistance over visible wavelengths at 85% transparency is ~70 Ω/sq. In vitro characterization shows that these CNT electrodes have electrochemical impedance comparable to those of gold and platinum without additional doping. Preliminary studies in transgenic hydra, a small cnidarian with a diffuse neural network, demonstrate good recording quality during simultaneous calcium imaging. These results indicate that CNT based flexible and transparent electrode arrays are a promising tool for optoelectronic interfaces in neuroscience.

1. Ledochowitsch et al., *Proc. Annu. Int. Conf. IEEE EMBS*, 2011
2. Park, et al., Nat. Commun., 2014
3. Kuzum, et al., Nat. Commun., 2014

Disclosures: **J.S. Yan:** None. **F. Vitale:** None. **D.G. Vercosa:** None. **K.N. Badhiwala:** None. **R. Headrick:** None. **J.T. Robinson:** None. **M. Pasquali:** None.

Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: NSF 1250104

Title: Microdevices for Scalable Neuroscience with Hydra

Authors: *K. N. BADHIWALA[1], D. L. GONZALES[2], D. G. VERCOSA[3], C. DUPRE[5], R. YUSTE[5], J. T. ROBINSON[4]
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Abstract: With a primitive nervous system of sparsely distributed neurons, the cnidarians provide a convenient model for whole brain activity mapping. Specifically, Hydra vulgaris is one of the emerging model organisms for discovering a complete cellular-level relationship between neural activity and behavior. For example, monitoring Hydra's naturalistic and stimulated behaviors can potentially reveal fundamental principles of sensory information processing. However, it is difficult to control the local environment in real-time and record the neural response because of Hydra's deformable and contractile body. Here, we present a suite of novel microfluidic chips capable of the first multimodal interrogation of these soft, deformable model

organisms. Specifically, we show devices that can immobilize Hydra for electrical and optical recording to correlate the neural activity with behavior. We also show devices that deliver chemical cues while behavioral responses are imaged. We further illustrate the potential of behavioral micro-arenas that enable locomotive and behavioral assays. Thus, microfluidic handling of Hydra provides a path toward scalable and high-throughput in vivo studies of neurobiology and neurological processes in these small model organisms.

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Poster

090. Electrode Arrays

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Program#/Poster#: 090.03/UU11

Topic: I.04. Physiological Methods

Support: NIH Program Grant P01-AI102852

NIH Program Grant P01-AI073693

Title: Altered ensemble dynamics in the CA1 region of the hippocampus in a murine model of CNS lupus

Authors: T. S. HUERTA[1], E. NASIRI[2], J. J. STROHL[3], *P. T. HUERTA[4]
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Abstract: Systemic lupus erythematosus (SLE) is a chronic multi-organ immune disorder that affects an estimated 1.5 million Americans. A particularly poorly understood facet of SLE is its neurological component, known as neuropsychiatric systemic lupus erythematosus (NPSLE), which effects 30–80% of SLE patients. NPSLE is associated with several neurological symptoms including cognitive impairment and memory dysfunction. Previous studies have implicated DNA-reactive antibodies (DNRABs) cross-reactive with GluN2A and GluN2B subunits of the NMDAR as contributors to the cognitive impairment found in mouse models of NPSLE. This study further substantiates this claim by applying novel behavioral tests and *in vivo* electrophysiological methods to investigate the effect of DNRABs on place cell dynamics in the CA1 region of the hippocampus. BALB/c mice (female, 6 weeks) were separated into two groups that were passively immunized over a 6-week period with MAP-DWEYS (DNRAB+ group, $n = 10$) and MAP-Core (DNRAB– control, $n = 10$). After 1 month, LPS was injected to abrogate the blood brain barrier. A month later, the mice were run in a clockmaze working memory (CMWM) task. During each trial, the mouse was given 60 sec to escape a paddling pool

(diam., 75 cm) with 11 decoy exits and one true exit. The test ran 3 days, 4 trials per day, with a different true exit each day. Representative mice were selected from the CMWM task (DNRAB+, n = 3, DNRAB–, n = 4), and implanted with custom tetrodes arrays targeting the CA1 region of hippocampus. *In vivo* electrophysiology recordings were conducted in an open field environment (four 15-min sessions) and a linear track (two 20-lap runs). Neural recordings were analyzed via spike sorting (Spike2), power spectral densities of network oscillations (Matlab), and place cell formation (NeuroExplorer). In the CMWM task, DNRAB+ mice displayed significantly higher escape latencies and lower use of spatial strategy than the DNRAB– controls, suggesting poorer spatial working memory. Place field analysis demonstrated remarkable differences in their place cell dynamics, with the DNRAB+ mice showing expanded place field size, reduced peak firing rate, and lower spatial information, when compared to DNRAB– mice. This study thus reveals a robust change in place cell properties when exposed to cross-reactive DNRABs. The behavioral and electrophysiological experiments suggest that a disruption in healthy place cell dynamics by DNRABs may be involved in the neurological symptoms of NPSLE, and offer a neural substrate for bioelectronic therapies aimed to alleviate NPSLE-related cognitive impairment.

Disclosures: **T.S. Huerta:** None. **E. Nasiri:** None. **J.J. Strohl:** None. **P.T. Huerta:** None.

Poster

090. Electrode Arrays

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Program#/Poster#: 090.04/UU12

Topic: I.04. Physiological Methods

Title: Decoding glucose levels from the cervical vagus nerve

Authors: *E. A. BATTINELLI[1,2], T. P. ZANOS[3], T. LEVY[3], C. BOUTON[3], S. CHAVAN[1], K. J. TRACEY[4,2,1,3]
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Abstract: The central nervous system plays a critical role in maintaining energy and glucose homeostasis. Systemic changes in the blood glucose levels activate afferent signals in the vagus nerve that travel to the brainstem resulting in an efferent response transmitted to the periphery, thus ensuring regulation of homeostasis. In our current study, vagus nerve signals generated in response to changes in systemic blood glucose levels were recorded and decoded. Feature analysis was used to extract glucose level information from these decoded signals. We surgically isolated the vagus nerves of anesthetized mice on cuff electrodes and recorded for 1 hour. The mice received an insulin or saline injection 30 minutes into the recording and blood glucose was

measured with a glucometer every 5 minutes. Using novel signal processing and feature extraction methods, we can isolate and track discrete neural features over time. We can accurately extract peripheral blood glucose levels from these neural features using lagged, multivariate linear regression. These correlations indicate that information in vagus nerve firing can be used to monitor changes in blood glucose levels. Functional and anatomical mapping of this reciprocal signaling will identify the properties of the neural circuit underlying the regulation of blood glucose levels, and provide a therapeutic target for the treatment of diabetes.

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Poster

090. Electrode Arrays

Location: Halls A-C

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Program#/Poster#: 090.05/UU13

Topic: I.04. Physiological Methods

Title: A novel signal processing framework for decoding systemic blood glucose levels from vagus nerve recordings

Authors: *T. LEVY[1], E. BATTINELLI[2], H. SILVERMAN[2], S. CHAVAN[2], K. TRACEY[3], C. BOUTON[3], T. ZANOS[3]
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Abstract: The central nervous system (CNS) plays a critical role in glucose homeostasis. Information about changes in systemic glucose levels is transmitted through the vagus nerve to the CNS. These neural signals are acquired from the surface of the vagus nerve and represent an aggregate of the activity of multiple nerve fibers. A decoding framework that extracts blood glucose levels from neural signals was developed. This is the first step toward creating an implantable device that can monitor and potentially control systemic blood glucose levels in diabetic patients.
We recorded neural signals from the cervical vagus nerve of 19 mice while simultaneously manipulating and tracking acute changes in blood glucose levels. Cardiac artifacts were isolated using wavelet decomposition and discarded. Compound Action Potentials (CAPs) were detected in the recorded signals via an adaptive threshold that adjusts its level per respiratory modulations. CAP waveforms were projected to a lower dimensional space using t-Distributed Stochastic Neighbor Embedding (t-SNE) and separated into clusters using Density-Based Spatial Clustering of Applications with Noise (DBSCAN). We hypothesized that clustering of the CAP waveforms would separate the activity of different groups of fibers/fascicles based on how they project to the surface of the nerve. Once separated, we extracted firing rate responses of these

CAP clusters and used them as our input signals for our lagged linear regression model with regularization to predict blood glucose levels. The CAPs and corresponding lags were selected on a per subject basis by first minimizing the out-of-sample (OOS) normalized mean squared error (NMSE) using a 3-fold cross-validation while searching over the space of combinations of up to 3 CAPS with corresponding lags of up to 15 minutes. The final CAPs and corresponding lags were selected based on the minimum in-sample NMSE from the set of CAPs/lags within 5% of the minimum OOS NMSE. All injection groups had median NMSE values below 0.06. The lag between the neural events and the changes in glucose were approximately uniform over the subjects.
These results strongly suggest we can accurately and effectively extract systemic glucose level based on the CAP firing rates from the cervical vagus nerve. Developing the capability to monitor blood glucose levels through neural signals is an important step in creating new emerging therapies within bioelectronic medicine using real-time implantable devices for diabetes.

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Poster

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Topic: I.04. Physiological Methods

Support: DARPA Grant HR0011-15-2-0016

Title: Vagus nerve activity: Methodology of recording in mice

Authors: *H. A. SILVERMAN[1,2], A. STIEGLER[1,3], T. TSAAVA[1], J. NEWMAN[1], B. E. STEINBERG[4], E. BATTINELLI[1,2], S. ROBBIATI[5], C. BOUTON[6], P. T. HUERTA[5], S. S. CHAVAN[1,6,2], K. J. TRACEY[1,2,6]
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Abstract: The vagus nerve plays an important role in the reflex regulation of visceral functions. Methodological and technological advances have identified that vagus reflex pathways also regulate immunity and inflammation. Recent studies using genetically modified mouse models has improved our understanding of the neural control of immune responses. However, mapping neural signals transmitted in the vagus nerve in mouse has been challenging due to the lack of

standardized experimental procedures. Here, we have standardized an experimental protocol to record compound action potentials transmitted in the vagus nerve in real time in baseline as well as stimulated conditions. The left cervical branch of the vagus nerve was isolated from the accompanying carotid bundle, and was placed over three custom-built silver hook electrodes (n=72) or in a commercially available bipolar sling cuff electrode (n=25) with 150 μm inner diameter. Cuff electrodes significantly reduced the background noise and increased the signal to noise ratio as compared to hook electrodes. Depth of isoflurane anesthesia and food intake significantly modulate the baseline vagus activity. 2.0%, 1.75% and 1.5% isoflurane with an oxygen flow of 1L/min were assessed; with the optimal isoflurane level for these recordings to be 1.75%. Non-fasted mice demonstrated a significantly higher number of total spikes over ($p<0.5$) as compared to the fasted group. However, no significant difference was observed in vagus neurograms between different mouse strains such as Balb/c and C57BL/6. Lastly, recording changes in vagus nerve activity in wild type and TLR4 receptor knock out mice revealed the receptor dependency of endotoxin mediated signals. Together these results present a novel method for recording vagus signals in mice.

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Poster

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NIH Program Grant P01-AI073693

Title: Dysfunctional ensemble dynamics in the CA1 region of the hippocampus in long-term sepsis survivors

Authors: *J. J. STROHL[1], T. S. HUERTA[2], P. T. HUERTA[3]
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Abstract: Sepsis is defined as a “life-threatening organ dysfunction caused by a dysregulated host response to infection” (Singer et al. JAMA 315:801 2016). Although the chance of surviving the initial shock has improved considerably, it has become apparent that long-term survivors suffer sepsis-related cognitive impairment. Studies of preclinical models of sepsis

consistently demonstrate deficits in spatial memory tasks and contextual fear conditioning. We have used the cecal ligation and puncture (CLP) procedure in mice to investigate the neural substrate of sepsis-induced memory impairment by studying place cell dynamics and hippocampal network oscillations. Male mice (C57BL/6, n = 20, BALB/c, n = 20) were subjected to fear conditioning, 6 weeks post-surgery, with CLP survivors showing clear deficit in contextual fear memory compared to Sham controls. Mice were implanted with tetrodes (C57BL/6, n = 6, BALB/c, n = 6) lowered into dorsal CA1 and, over the course of 7 days, were tested repeatedly in open field environments and linear tracks (20-min *Run* sessions interspersed with 10-min *Rest* sessions). Analysis included quantifications of mean and peak firing rates, place field size and stability, spatial information, as well as spectral power of the different bands in the local field potential (software: Cheetah, Spike2, NeuroExplorer, Matlab, Chronux). Examination of CLP survivors with poor contextual memory revealed larger place field areas (Sham, 335.5 ± 182.5 cm^2, CLP, 516.9 ± 197.3 cm^2, $p = 1.2x10^{-10}$, D = 0.5, Kolmogorov Smirnov test), increased delta power (1-4 Hz, normalized medians, Sham 109.6, CLP, 638.6, p = 0.002, Z = 3.11, Mann-Whitney [MW] test), decreased theta power (4-12 Hz, Sham, 92.9, CLP, 28.8, $p = 9.3x10^{-5}$, Z = 3.91, MW test), and decreased low-gamma power (30-50 Hz, Sham, 76.9, CLP, 27.9, $p = 8.1x10^{-5}$, Z = 3.94, MW test). Our results suggest that the dorsal CA1 network of sepsis survivors is disrupted, in terms of network oscillations and place cell dynamics, and this may constitute a neural substrate for bioelectronic therapies aimed to alleviate sepsis-related cognitive impairment.

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Poster

090. Electrode Arrays

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Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)

Title: Galantamine alleviates the inflammatory state and insulin resistance in patients with the metabolic syndrome

Authors: *V. A. PAVLOV[1], F. M. CONSOLIM-COLOMBO[2,3], C. T. SANGALETI[2,4], J. M. MOTTA[2], F. O. COSTA[2], T. L. MORAIS[3], M. C. IRIGOYEN[2], L. A. BORTOLOTO[2], C. EDUARDO ROCHITTE[2], H. F. LOPES[2,3], Y. TOBI HARRIS[5], S. K. SATAPATHY[6], P. S. OLOFSSON[7], M. AKERMAN[8], S. S. CHAVAN[1], M. MACKAY[8], D. BARNABY[10], M. L. LESSER[8], J. ROTH[8], K. J. TRACEY[9]
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Abstract: The metabolic syndrome (MetS) is an obesity-driven disorder of pandemic proportions that significantly increases the risk of type 2 diabetes and cardiovascular disease. Pathophysiological mechanisms are poorly understood, though inflammation has been implicated in MetS pathogenesis. We have previously shown the anti-inflammatory effects of galantamine, a centrally-acting acetylcholinesterase inhibitor clinically-approved for the treatment of Alzheimer's disease. The aim of this study was to assess the effects of galantamine on inflammatory, metabolic and cardiovascular indices in subjects with MetS. In a randomized, double-blind, placebo-controlled trial, subjects with MetS (30 per group) received oral galantamine 8 mg daily for 4 weeks, followed by 16 mg daily for 8 weeks or placebo. The primary outcome measures were circulating levels of cytokines and adipokines with an important role in mediating the chronic inflammatory state in MetS. Secondary endpoints included body weight, fat tissue depots, plasma glucose, insulin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), cholesterol (total, HDL, LDL), triglycerides, blood pressure, heart rate and heart rate variability (HRV). Galantamine treatment resulted in lower plasma levels of pro-inflammatory molecules TNF (-2.57 pg/ml [95% CI -4.96 to -0.19]; *P*=0.035) and leptin (-12.02 ng/ml [95% CI -17.71 to -6.33]; *P* <0.0001), and higher levels of anti-inflammatory molecules adiponectin (2.71 μg/ml [95% CI 1.93 to 3.49]; *P*<0.0001) and IL-10 (1.32 pg/ml, [95% CI 0.29 to 2.38]; *P*=0.002) as compared to placebo. Galantamine also significantly lowered plasma insulin and HOMA-IR values, and altered HRV. In conclusion, low-dose galantamine alleviates the inflammatory state and insulin resistance in MetS subjects. These findings support further study of galantamine in MetS therapy.

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Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: DARPA Grant HR0011-15-2-0016

Title: Selective electrical stimulation of vagus nerve induces specific cytokine response

Authors: *T. TSAAVA[1,2], M. E. ADDORISIO[1,2], J. E. NEWMAN[1], C. BOUTON[2], K. J. TRACEY[1,2], S. S. CHAVAN[1,2]
[1]Lab. of Biomed. Sci., [2]Ctr. for Bioelectronic Med., Feinstein Inst. at Northwell Hlth., Manhasset, NY

Abstract: Neuro-immune communication and neural circuits regulating immunity have been therapeutically explored in preclinical models and recently in human clinical trials. Implantable bioelectronic devices that mediate electrical vagus nerve stimulation to activate inflammatory reflex are being increasingly used as a treatment strategy to target the inflammatory diseases. These treatments take advantage of the neural circuitry to deliver anti-inflammatory signals to target organs. In the current study, we analyzed changes in circulating cytokine levels in response to electrical stimulation of the vagus nerve using different pulse parameters. The cervical vagus nerve was isolated in adult male Balb/C mice and subjected to asymmetrical balanced biphasic pulse stimulation using bipolar cuff electrodes. The stimulation parameters were: frequency 30-200 Hz, amplitude 50-750uA, pulse width 50-250us and stimulation duration 4 minutes. After 2 hrs, circulating levels of IL-1β, IL-6, TNFα, IL-10 and KC/GRO were quantitated. Serum cytokine levels changed significantly in amplitude dependent and pulse-width dependent manner. Specifically, the most significant increases were observed with 50uA ($P \leq 0.0001$) and 200uA ($P \leq 0.0001$) pulse at 30Hz and 100Hz frequencies, and with a 750uA pulse at 30Hz. Moreover, an additional increase in the cytokine levels was observed with a 250us square pulse. Together, these studies demonstrate that systemic cytokine levels can be modulated by selectively stimulating the vagus nerve using specific combinations of frequencies and amplitudes. This study was funded in part by DARPA (HR0011-15-2-0016).

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Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: Chad Bouton Startup package at Feinstein

Title: A novel high-density flexible peripheral electrode for acute and chronic neural interfacing for real time diagnostics

Authors: *M. STRAKA[1], L. GOLDMAN[2], T. TSAAVA[3], H. A. SILVERMAN[4], T. P. ZANOS[5], S. S. CHAVAN[6], K. J. TRACEY[7], C. LI[8], L. RIETH[9,8], C. BOUTON[10], H. SOHAL[11,8]
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Abstract: Real time diagnostics requires the ability to continuously sense information (e.g. from peripheral nerves) and correct aberrant activity through recording and stimulation methods with the use of implanted electrodes. Many current electrode designs have low channel counts, allowing the capture of only a certain number of compound action potentials (CAPs) to any given pharmacological challenge of the nerve or from genetic mouse models of disease. Further, many of these implants cannot be successfully implanted chronically due to their size and damage to the nerve long-term.
Here we present a novel, high density, customizable, flexible electrode array for both acute and chronic monitoring and stimulation of the mouse cervical vagus nerve. The electrode is based on thin film parylene-C technology and has an incorporated ribbon cable with an appropriate connector to allow anchoring of the electrode to the skull. The interfacing electrode is very thin and inherently flexible, allowing for optimal interfacing and wrapping around small diameter peripheral nerves without the pressure associated with bulky silicone cuffs. We microfabricated various recording and stimulation site areas for broad and focal CAP isolation from the nerve. Sites are also spatially oriented to reduce the similarity (redundancy) in the measured signal, ensuring that every site is capturing unique information.
We have validated the electrode through evaluating the recording performance showing good CAP detection with high fidelity recording signal during specific challenges (e.g. TNF and IL-1β) of markers relevant for many inflammatory diseases. Stimulation from the electrode showed

marked physiological effects through nerve stimulation and can be used for chronic high frequency block to attenuate activity in the nerve.
Such platform technologies can be used to enhance the dimensionality of the information obtained in various experimental disease models, potentially leading to a greater understanding of the molecular and electrical interplay in various disease states for real time diagnostics and subsequent treatment.

Disclosures: **M. Straka:** A. Employment/Salary (full or part-time):; Feinstein Institute. **L. Goldman:** A. Employment/Salary (full or part-time):; Feinstein Institute. **T. Tsaava:** A. Employment/Salary (full or part-time):; Feinstein Institute. **H.A. Silverman:** None. **T.P. Zanos:** A. Employment/Salary (full or part-time):; Feinstein Institute. **S.S. Chavan:** A. Employment/Salary (full or part-time):; Feinstein Institute. **K.J. Tracey:** A. Employment/Salary (full or part-time):; Feinstein Institute. **C. Li:** A. Employment/Salary (full or part-time):; Feinstein Institute. **L. Rieth:** A. Employment/Salary (full or part-time):; Feinstein Institute. **C. Bouton:** A. Employment/Salary (full or part-time):; Feinstein Institute. **H. Sohal:** A. Employment/Salary (full or part-time):; Feinstein Institute.

Poster

090. Electrode Arrays

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Title: Chronic evaluation of a novel flexible cuff like electrode for peripheral nerve interfacing in the mouse

Authors: T. TSAAVA[1], M. STRAKA[2], A. S. CARAVACA[4], L. GOLDMAN[2], G. RIGGOTT[5], S. S. CHAVAN[2,3], K. J. TRACEY[2,3], C. BOUTON[2], P. S. OLOFSSON[6], E. S. BOYDEN[5], *H. SOHAL[2]

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Abstract: Bioelectronic medicine is an initiative where neural signals are used to sense biomarkers of disease and subsequently decoded to inform electrical stimulation of effective targets to relieve disease symptoms and restore homeostasis. Many preclinical disease models rely on transgenic mouse lines. Currently, there exists no effective electrode implant to record and stimulate the peripheral nerves chronically in the mouse. The implicit design challenges of interfacing with the mouse cervical vagus nerve include successfully wrapping with a cuff that causes minimal damage while ensuring good electrical contact with the nerve, which is around 100 μm in diameter. Further, routing the connections from the electrodes to an appropriate connector, without placing unnecessary tethering forces on the nerve to damage it over time is another tremendous challenge. Recently we showed an effective implant for recording and stimulation of mouse vagus nerve through initial acute testing of novel flexible devices. Initial implantation of such devices also showed the feasibility of this design in chronic interfacing with peripheral nerves in the mouse (SfN 2016, *Paper Submitted*). The flexible array was microfabricated on an 8 μm layer of highly biocompatible parylene configured with 16 sites, and designed to interface with the diameter of the mouse cervical vagus nerve~ 100 um. The array contained a ribbon cable mating to a widely used commercial connector (Omnetics, USA). Here, we report on the chronic implantation and evaluation of the devices in the mouse. Devices were implanted and the flexible cuff was secured around the mouse cervical vagus nerve. The electrode connector was attached to the skull, through an interfacing ribbon cable to obtain reliable connection to our electrode array over time. In-vivo Impedance measurements at 1 kHz indicate that values remained stable across the chronic implantation period, showing that the integrity of the device was preserved. Post-hoc histology of the nerve showed reduced foreign body responses compared to controls, evaluated > 6 months post-implant. Chronic recordings were analyzed in terms of peak-to-peak signal, noise and SNR of obtained compound action potentials over the implantation period. These initial results show the feasibility of using flexible interfacing strategies to reduce damage to the mouse peripheral nerve and increasing recording longevity. The acquisition of such chronic neural signatures are important in understanding neural and molecular mechanisms, especially in mouse models of disease, to inform future bioelectronic treatment strategies.

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Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: DARPA W911NF-09-1-0125

Title: Decoding mouse vagus nerve activity for cytokine discrimination

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Abstract: The human body has built-in biological sensors that continuously monitor organ function and detect changes in related biomarkers. It has been shown the nervous system senses and regulates the inflammatory response in real time. The purpose of this study is to record neural signals emanating from these sensors and propagating through peripheral nerves. This could be used them to diagnose inflammatory, infection and trauma states. These neural signals are usually acquired from surface nerve electrodes and represent an aggregate of the activity of multiple nerve fibers or fascicles. Moreover, they are prone to various sources of noise (cardiac, respiratory, instrumentation). Here we present a methodological framework that detects, isolates and relates this neural activity to changes in levels of cytokines, substances that are directly related to our immune response. The methodology manages to successfully discriminate changes between two specific cytokines, tumor necrosis factor (TNF) and interleukin 1β (IL-1β), using neural signals as its input. The vagus nerve was surgically isolated in anesthetized BALB/C mice and cuff electrodes were placed on the nerve. Neural recordings were acquired for 90 minutes, while two alternating intraperitoneal injections of TNF or IL-1β were performed 30 minutes apart. Control animals were injected with saline following the same design. Cardiac artifacts were isolated using wavelet decomposition and Compound Action Potentials (CAPs) were detected in the recorded signals via an adaptive threshold that adjusts its level per respiratory modulations. CAP waveforms were projected to a lower dimensional space and separated in clusters using unsupervised clustering methods. CAP waveforms clustering separated the activity of different groups of fibers/fascicles based on how they projected to the surface of the nerve. Once separated, firing rate responses of these CAP clusters were extracted and used as the input signals to the classification algorithm. A 3-fold cross-validated naïve Bayes classifier was used to discriminate between no injection, IL1 or TNF injection states, using responsive neural firing

rates as the input. 74% and 45% of the animals responded to IL1/TNF and TNF/IL1 injection sequences respectively, with only 29% responding to our control saline injections. Mean decoding accuracy exceeded 80% out-of-sample true positives. These results showcase that we can discriminate between two cytokines based on the CAP firing rates from the cervical vagus nerve. This is a first step towards developing the capability to monitor cytokine levels in real time and creating new emerging therapies for bioelectronic medicine.

Disclosures: T.P. Zanos: None. **H.A. Silverman:** None. **T. Levy:** None. **E.A. Battinelli:** None. **S.S. Chavan:** None. **K.J. Tracey:** None. **C. Bouton:** None.

Poster

090. Electrode Arrays

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 090.13/UU21

Topic: I.04. Physiological Methods

Title: Nerve cuff electrodes for electrically interfacing with the peripheral nervous system

Authors: *M. SCHUETTLER[1], C. BIERBRAUER[1], R. PFEIFER[1], M. ULLOA[1], C. HENLE[1], J. RICKERT[1,2]
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Abstract: Bioelectronic medicine focusses on treating conditions such as rheumatic arthritis, diabetes, hypertension, infertility and others by electrically modulating disordered circuitry of the peripheral nervous system. For doing so, the targeted nerves need to be connected to an electrical interface. Cuff electrodes provide such an interface. They consist of an electrically insulating cylinder installed around the nerve having one or multiple electrical contacts facing towards the neural tissue. Passing an electrical current through the contacts will either artificially excite fibers of the nerve, inhibit natural signal traffic to travel along the nerve or modulate the natural neural signals. We developed a flexible method for making multi-contact nerve cuffs for nerve diameters ranging from 0.1 mm to 10.0 mm diameter applying laser-micromachining of medical grade silicone rubber and high-purity platinum-iridium foil. Depending on the nerve diameter and the location of implantation (deep cavities or rather superficial locations) the cuff closure mechanism has to be adapted. The closure mechanism is responsible for 1.) a reliable fixation of the cuff to the nerve, preventing it from slipping off, and 2.) ensuring electrical insulation between the inside (nerve) and the outside (surrounding tissue) area of the cuff, which is desired for electrical stimulation, and absolutely crucial for electrical recording of nerve signals. Four closure mechanisms have been developed: a) Buckle and belt closure for very small nerves, so called 'sling cuffs', b) Self-closing split-cylinder with dual-sealing lips, called 'tunnel cuffs' c) Self-closing split-cylinder cuffs without extra seals and d) self-wrapping spiral cuff

electrodes.
The cuffs have been used extensively in animal studies, providing stable electrical stimulation and recording properties, as well as in human studies for fascicle-selective nerve stimulation.

Disclosures: **M. Schuettler:** None. **C. Bierbrauer:** None. **R. Pfeifer:** None. **M. Ulloa:** None. **C. Henle:** None. **J. Rickert:** None.

Poster

090. Electrode Arrays

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: I.04. Physiological Methods

Support: DFG, grant number EXC 1086

Title: Transparent electrode materials for multimodal stimulation and measurement techniques

Authors: *L. ASPLUND[1], C. BOEHLER[2], F. OBERUEBER[1]
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Abstract: Microsystems-engineered implants make it possible to perform electrical recording and stimulation of neuronal populations in vivo at high spatial resolution. Such techniques gained in popularity during recent years and enable studies on the living nervous systems and its diseases. It has in addition become increasingly common to combine these techniques with complementary methods, next to the purely electrical measurements. In genetically modified animal models it is possible to stimulate neurons with optical techniques ideally making it possible to trigger network activity optically and simultaneously record electrically. Furthermore, two-photon microscopy can be used to monitor tissue reactions in vivo meaning cells that are electrically recorded from can at the same time be visualized via their specific fluorescence. For these modalities to be combinable with the microelectronic probes, new requirements on their construction materials are introduced which previously have not been considered. Next to qualities such as low impedance and high charge injection capacity, electrodes must in addition have favourable properties not to interfere with the optical techniques applied. Low photo-induced currents, insignificant auto-fluorescence and optical transparency of the complete probe are attractive to facilitate experiments and analysis.
We here investigate a variety of electronic materials and analyse their suitability to act as neural microelectrodes integrated in a fully transparent neural probe. Several variations of the conducting polymer poly(3,4-ethylene dioxythiophene) (PEDOT)/polystyrene sulphonate are investigated, next to indium tin oxide (ITO) and carbon based electrode materials. The respective contributions of the conducting substrate, and the electrode coating material, to the

photoelectrical artefact are analysed. Furthermore the auto-fluorescence and absorbance of materials is quantified in order to analyse its compatibility with fluorescence imaging. In summary, we thereby aim to present a materials based strategy for making transparent stable and artefact free electrodes available in the future, without sacrificing the low impedance and high charge injection necessary for enabling high quality electrophysiological measurements in vivo.

Disclosures: L. Asplund: None. **C. Boehler:** None. **F. Oberueber:** None.

Poster

090. Electrode Arrays

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 090.15/UU23

Topic: I.04. Physiological Methods

Support: BrainLinks-BrainTools

Title: Long-term stability of implanted high density polyimide ECoG arrays

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Abstract: The technology for miniaturization of bioelectronics is making great progress, and the interest for high density electrode recordings in the neural systems is continually increasing. High density recording of, e.g., the cortical activity could help scientists to elucidate the language of the brain and further increase our understanding of the behavior of the cells in the neural system. Furthermore, a high density electrode implant would also increase the possibility to choose specific electrodes, e.g. in the proximity of the desired neural target, or active sites instead of silent. Also, the ability to map larger surface areas with high density arrays could help growing the understanding for the connectivity between different regions in the brain. In our group we have developed several structures based on the polymer polyimide, which is a flexible, stable and biocompatible polymer, therefore excellent for neural probes, especially for long-term applications with high demands on reliability. Designs have been targeted to animal models of turtles, rats, ferrets, cats and macaque monkeys. Modular, finger-based designs adapted well to the two-dimensionally curved structure of the brain surface even though the substrate material itself is not stretchable. Electrode size and pitch have been adapted to the size of the target structures. Array variations comprised 36, 64, 96, 192 and 252 electrode sites. Several high density ECoG arrays have been fabricated and implanted into primates. These showed good

long-term stability and both single-unit activity, as well as multi-unit activity and local field potentials could be recorded via platinum and iridium oxide thin-film metal sites. Signal-to-noise ratios were sufficiently high over months and degraded only slowly. Results on stability and functionality are promising and consistent with other translational studies on peripheral nerves.

Disclosures: **R. Liljemalm:** None. **P. Fries:** None. **C.M. Lewis:** None. **A.K. Engel:** None. **F. Pieper:** None. **G. Engler:** None. **E. Fiedler:** None. **T. Stieglitz:** None.

Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: DFG, grant no. EXC 1086

European Union's Seventh Framework Program (FP7/2007-2013) under grant agreement n°600925 (NeuroSeeker)

Title: Optical tools with integrated light sources for optogenetics - An analysis of different system approaches

Authors: ***M. SCHWAERZLE**[1,2], S. AYUB[1], O. PAUL[1,2], P. RUTHER[1,2]
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Abstract: This paper analysis and compares specifications of optical tools with integrated light sources dedicated for optogenetic applications. Besides the demands given by the scientific goal, animal model and experimental setup, the decision on the system approach is influenced by design and fabrication considerations as well as the electrical, optical and thermal properties of the miniaturized tools. In general, possible light sources to be integrated are light emitting diodes (LED) or laser diodes (LD), both available as unpackaged bare chips (size approx. 300×300 µm^2). The following analysis is based on microfabricated neural devices recently designed and fabricated by our group.
In general, these optical devices can be used to either illuminate the brain surface or deeper brain regions, thus enabling a position and depth-controlled tissue stimulation, respectively. Light emitting spots down to 13×20 µm² are realized using polymeric waveguides (WG) integrated on silicon (Si) probe shafts directly coupled to LD chips. Larger illumination areas are covered by tools with LED chips (emitting area 190×230 µm²) and arrays thereof. Radiant emittances exceeding 1000 mW/mm² are obtained with LD-WG systems. Lowered emittances can be set by adapting the duty cycle (DC) of the pulse-width-modulated LD current.

With respect to the potential temperature increase of the implanted probes, the operating parameters of the integrated light sources and their power consumption in a wireless system have to be chosen carefully and preferably monitored with integrated temperature sensors.
The LED-based systems are available on highly flexible substrates enabling bending radii down to 1 mm for brain surface applications as well as an insertion into the cochlea. For the insertion into deeper brain areas the systems are stiffened by Si structures, simultaneously restricting the light-emitting area by miniaturized apertures. Likewise, micromachined Si housings are used to align implantable optical fibers guiding light from LED chips to the stimulation sites.
Additionally, the WGs combined with LD chips are fabricated directly on Si substrates enabling the simultaneous integration of recording sites on the same probe.
While bare LED chips with single-sided contact pads are available at various wavelengths (e.g. 460 nm, 527 nm), obtaining unpackaged LD chips was found to be rather difficult in view of their integration into neural probes. While Kampasi et al. (2016) applied LD chips emitting at 405 nm potentially causing light absorption in the polymeric WG, commercially available LD chips were so far limited to wavelengths of 635 nm and 650 nm.

Disclosures: **M. Schwaerzle:** None. **S. Ayub:** None. **O. Paul:** None. **P. Ruther:** None.

Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: DFG Grant EXC1086: Brainlinks-BrainTools

Title: Laser-induced carbon microelectrode arrays for chronic neural applications

Authors: *T. STIEGLITZ, A. OLIVEIRA, D. ASHOURI, M. VOMERO, M. EICKENSCHEIDT
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Abstract: In the field of neural prostheses, much attention has lately been given to the long-term performance not only of the electronic components but also of the parts directly interfacing with the nervous system. Neural interfaces have, in fact, a critical role in chronic applications, where they have to outlast the highly humid and oxidative body environment without undergoing delamination, corroding and without losing their functionality over time. Among all, carbon has been proved to be the material with the highest potential to contemporary serve as biomaterial for recording nerve cells activity, electrically stimulating them and, in addition, for selectively detecting the presence of neurotransmitters or other electrically active biomolecules. However,

the feasibility of the fabrication method - with respect to process complexity and cost - is a factor of great importance and it is not always easy to accomplish with carbon electrodes. In this work, we present a new method to manufacture thin-film microelectrode arrays (MEAs) with laser-induced carbon active sites made from parylene c coatings on platinum iridium tracks. Such MEAs are manufactured without the need for cleanroom and MEMS processes. Prototypes of these carbon electrodes were evaluated first *in vitro* in hydrogen peroxide to mimic the post-surgery oxidative environment due to the acute inflammatory reaction to the implant. Electrodes were stimulated using biphasic pulses to prove their stability under electrical stress and testes with respect to their biosensing capabilities on different concentrations of dopamine in PBS. Results show that our laser-induced carbon electrodes do not deteriorate under chemical and electrochemical loads. They were able to detect different dopamine levels in vitro. These new laser-induced carbon electrodes show promising potential to successfully be implanted *in vivo* and be used for long-term neural applications for recording, stimulation and biochemical sensing.

Disclosures: T. Stieglitz: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CorTec GmbH, Neuroloop GmbH. F. Consulting Fees (e.g., advisory boards); CorTec GmbH, Neuroloop GmbH. **A. Oliveira:** None. **D. Ashouri:** None. **M. Vomero:** None. **M. Eickenscheidt:** None.

Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: INOPRO (BMBF, 16SV7656)

BrainLinks-BrainTools (DFG, EXC1086)

Title: Restoring natural sensory feedback in amputees via electrical stimulation after targeted muscle reinnervation

Authors: *C. F. PASLUOSTA, P. KIELE, A. RESCH, T. STIEGLITZ
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Abstract: The loss of a limb permanently disrupts daily living activities. Prosthetic devices are an alternative to partially circumvent this disability. The lack of sensory feedback of current prosthetic options limits their acceptance and usability rate. In the upper limb, somatosensory percepts are essential for proper object manipulation, while in the lower counterparts proprioceptive and cutaneous sensations are required to maintain balance and stable gait.

Restoral of sensory feedback also improves the sense of embodiment of prosthetic limbs, which positively impacts user satisfaction. The introduction of surgically targeted muscle reinnervation (TMR) led to promising outcomes in terms of controllability of prosthetic devices, and in providing a novel channel to restore sensory information. TMR consists on re-routing the remaining peripheral nerves from the amputee's stump to the chest area. After transferring the nerves into the chest, afferent and efferent fibers reinnervate the hosting muscles, amplifying the signals from the efferent pathways, and providing a more selective channel for activating afferent fibers. We have previously demonstrated that electrical stimulation of peripheral nerves using implanted intrafascicular electrodes elicits natural sensory feedback during real-time, bidirectional control of a prosthetic hand. In this study, we propose that after TMR, the afferent reinnervated fibers can be electrically stimulated to restore natural somatosensations. We further propose that this stimulation can be provided wirelessly by capacitive coupling through the chest skin, eliminating the need for percutaneous cables and implanted electronics. An electrode implanted in the inner side of the skin picks up a portion of the current flowing inside bodily tissue when two surface electrodes located in the vicinity of the reinnervated muscles are electrically stimulated. Practically, this implanted electrode is electrically connected to the fibers reinnervated in the chest muscles such to transfer the collected current and depolarize the surrounding nerve axons. We simulate different stimulation paradigms of electrical currents travelling through the skin to the sensory fibers. Activation outputs of reinnervated afferent fibers of the peripheral nerves are then analyzed using a hybrid model of the electrical field generated by the stimulation. The outcomes of this proof-of-concept prototype as well as the implication of this novel technique for restoring natural sensory feedback in the amputee are discussed.

Disclosures: **C.F. Pasluosta:** None. **P. Kiele:** None. **A. Resch:** None. **T. Stieglitz:** None.

Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: NIH Grant 1R21NS094900 (NINDS)

Department of Biomedical Engineering, Michigan State University

Department of Electrical and Computer Engineering, Michigan State University

Title: Alterations in ion channel expression surrounding implanted microelectrode arrays

Authors: *J. W. SALATINO, M. H. DRAZIN, E. K. PURCELL
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Abstract: Implanted devices capable of “read-out” and “write-in” of brain signaling have created a renaissance in the study and treatment of neurological injuries and diseases. These technologies are becoming increasingly multi-functional and sophisticated, including electrical, chemical, and optical modes of interfacing with improved spatiotemporal resolution. However, poor biological integration remains a significant barrier to the longevity and stability of sensors and actuators implanted in the brain. Recently, our laboratory showed that the expression of glutamatergic and GABAergic synaptic transporters are altered locally to the implanted interface, suggesting that changes in excitatory/inhibitory tone occur surrounding implants over time (Salatino 2017). Here, we report that shifts in voltage-gated sodium and potassium ion channel expression parallel our previous results, supporting the hypothesis that changes in local intrinsic excitability accompany chronic devices. Sixteen-channel “Michigan-style” microelectrode arrays (Neuronexus) were bilaterally implanted in M1 of adult male Sprague-Dawley rats for pre-determined time points (1 day, 1 week, 6 weeks, 12 weeks). Recording quality was assessed from bi-weekly recording sessions, where the number of units, signal-to-noise ratio, unit amplitude, and amplitude of the local field potential were assessed over the study duration. At the terminal endpoint, subjects were perfused with paraformaldehyde and brains were processed for immunohistochemistry. Samples were imaged with a confocal microscope and analyzed using an intensity profiling MATLAB script (Salatino 2017). Results show a progression from profoundly increased local sodium channel expression to heightened potassium channel expression over time. We currently are assessing the cellular specificity of labeling with glial and neuronal markers. Our observations suggest an initial period of hyperexcitability surrounding devices followed by hypoexcitability at chronic time points. The findings reveal a novel mechanism underlying the instability and signal loss which typically occur with chronically implanted recording arrays, as well as a previously-unreported form of plasticity associated with brain implants.

Disclosures: J.W. Salatino: None. **M.H. Drazin:** None. **E.K. Purcell:** None.

Poster

090. Electrode Arrays

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Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: I.04. Physiological Methods

Support: HHMI

Title: Enhanced glass pipette micro-electrodes for multi-modal electrophysiology

Authors: *D. L. HUNT, M. BARBIC
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Abstract: Technology enabling the measurement of intracellular neural activity has been critical for investigating fundamental aspects of neuronal function. Glass patch-pipettes are the most widely utilized electrode type for intracellular recording, enabling detection of sub-threshold events and precise manipulation of the membrane potential. Most intracellular recording studies are performed *in-vitro* where neurons are accessible, yet where the neural circuitry and "biochemical context" have been drastically altered by slicing. This confound occludes measurement of brain-state dependent circuit dynamics that would otherwise be present *in-vivo*, where the brain region of interest can often be difficult to access. Moreover, neural circuits *in-vivo* have unique computational capabilities that emerge from the collective properties of individual units, giving rise to signals typically extracted from the local field potential (LFP). With the ability to capture the LFP, extracellular recording technologies have provided valuable complementary information to intracellular studies. However, sub-threshold fluctuations cannot be detected by extracellular recoding methods, making the combination of intra + extracellular recording technologies of broad interest to better understand the relationship between single-unit and collective properties. A significant obstacle in combining these two electrophysiology methods is the incompatibility of their fabrication methods, where glass pipettes are made in a one-at-a-time process that results in a curved probe structure, while most extracellular electrodes are fabricated in a planar lithographic process. Here we describe a suite of novel approaches that include soft lithography and "electro-less" plating to integrate extracellular recording sites that conform to the curved surface of glass pipettes. This technology allows for the reproducible micron-scale positioning of flexible extracellular electrodes, optical waveguides, and chemical sensors (with 5-20 micron intra-to-extra site distance) onto any glass pipette geometry of user preference. These minimally invasive integrated recording devices are capable of simultaneous intracellular whole-cell patch clamp, and multi- or single-site extracellular recording. We extend this versatile platform to include capabilities for optogenetics as well as electrochemistry, and demonstrate their multi-modal functionality *in-vivo*.

Disclosures: D.L. Hunt: None. **M. Barbic:** None.

Poster

090. Electrode Arrays

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 090.21/UU29

Topic: I.04. Physiological Methods

Title: Robust, highly customizable, and economical multi-channel electrode for chronic multi-unit recording in behaving animals

Authors: *M. SHIRAISHI, Y. TATEYAMA, K. OYAMA, M. OHI, T. IIJIMA, K.-I. TSUTSUI
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Abstract: Understanding how activities of neurons produce complex animal's behavior is one of the central issues of neuroscience. Multi-unit recording has been one of the most widely used techniques to investigate the correlation between multiple neuronal activities and behavior. Recent developments of various types of multi-channel electrodes have enabled recording from a large number of neurons simultaneously, which would help reveal information coding by neuronal ensembles. However, a common problem in the current multi-channel electrodes is that they are not sufficiently robust for repeated penetrations into the dura mater of the animal brain. In this study, we developed a novel multi-channel electrode with adequate physical strength to penetrate a thickened dura mater. This electrode consisted of a standard tungsten needle electrode with tungsten microwires attached onto it. Furthermore, it has high customizability and costs much less than typical commercially available multi-channel electrodes. Using this electrode, we could record neuronal signals for several months in behaving rats and monkeys without removing the dura mater, which leads to reduction of the risk of inflammation, infection, or brain herniation. We also found that the impedance of the electrode tip remained relatively stable after repeated use. These results suggest that this low-cost multi-channel electrode would be a useful tool for chronic recording in behaving animals.

Disclosures: M. Shiraishi: None. **Y. Tateyama:** None. **K. Oyama:** None. **M. Ohi:** None. **T. Iijima:** None. **K. Tsutsui:** None.

Poster

090. Electrode Arrays

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Topic: I.04. Physiological Methods

Support: UT BRAIN Seed grant award #365459

CDMRP award W81XWH-16-1-0580

NIH R01NS082518

NIH R01EB011556

Title: Concurrent optical imaging and extracellular recording for longitudinal studies of behaving brain

Authors: *L. LUAN[1], C. SULLENDER[2], Z. ZHAO[2], X. LI[2], H. ZHU[2], X. WEI[2], J. J. SIEGEL[3], R. CHITWOOD[3], A. DUNN[2], C. XIE[2]
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Abstract: Simultaneous intracortical electrical recording and optical imaging promise combinative advantages from the two complementary methodologies including large field of view, high-spatial resolution and multi-modality from optical imaging, and high temporal resolution at non-superficial tissue depths from electrical recording. However, combined implementation of both methods for longitudinal studies of behaving brain has been rare, in large part due to the lack of electrophysiological methods that record individual neurons at minimal tissue invasiveness while maintaining convenient chronic optical access. Here we demonstrated in mouse models that a novel type of intracortical microelectrodes, the ultraflexible nanoelectronic threads (NETs), enabled chronic multimodal neural platform that combines electrical recording of neural activity and optical imaging. Using genetically encoded calcium indicator GCamp6 by viral transduction in the somatosensory cortex, we performed repeated two-photon imaging of Ca^{2+} transients simultaneously with electrical recording of action potentials. By combining spatially resolved electrical recording with laser speckle contract imaging, we demonstrated simultaneous mapping of neural activity and cerebral blood flow (CBF) over chronic time scales in a targeted photothrombosis model, including the propagation of peri-infarct depolarizations, the chronic progression of ischemia, and the reperfusion and revived neural activity days after the initial insult. These results show that the NETs enable novel multimodal neural platform for longitudinal, multimodal interrogation of behaving brain that can be applied to a variety of basic and applied neuroscience studies.

Disclosures: **L. Luan:** None. **C. Sullender:** None. **Z. Zhao:** None. **X. Li:** None. **H. Zhu:** None. **X. Wei:** None. **J.J. Siegel:** None. **R. Chitwood:** None. **A. Dunn:** None. **C. Xie:** None.

Poster

090. Electrode Arrays

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Program#/Poster#: 090.23/UU31

Topic: I.04. Physiological Methods

Title: Affordable open-source micro-drive array for chronic in-vivo recording of rodent neural systems

Authors: *J. H. WHEAR, G. M. MUIR
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Abstract: Among the many challenges of chronically recording neuronal activity from multiple cells is the cost of purchasing or producing drives that fit the functionality and spatial requirements required for individual recording demands. These challenges are even greater when employing such technologies in the instruction of undergraduates or during research at under-funded institutions. Here, we have created a customizable microdrive array that allows for individual driving of 8 tetrodes (32 electrodes) with a drive body that is entirely 3D-printable using a standard 3D printer. This is assembled using cheap and easy to source materials, and is compatible with the open-ephys system. The quick turn-around time and cheap cost of our microdrive allows for basic in-vivo electrophysiology to be feasible for undergraduate or teaching laboratories.

Disclosures: J.H. Whear: None. **G.M. Muir:** None.

Poster

090. Electrode Arrays

Location: Halls A-C

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Topic: I.04. Physiological Methods

Support: ALW grant 823-02-010

ERC Grant 339490

Title: 3D printing and modelling of customized implants and surgical guides for non-human primates

Authors: *X. CHEN[1], J. K. POSSEL[3], C. WACONGNE[3], A. VAN HAM[3], P. C. KLINK[2], P. R. ROELFSEMA[4]
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Abstract: Background: Primate neurobiologists use chronically implanted devices such as pedestals for head stabilization and chambers to gain access to the brain and study its activity. Such implants are skull-mounted, and made from a hard, durable material such as titanium. Commercial-off-the-shelf solutions typically come with a uniform, flat base, preventing them from sitting flush against the curved surface of the skull. This leaves gaps for fluid and tissue ingress, increasing the risk of microbial infection and tissue inflammation, as well as implant loss. New method: Here we present a low-cost method of creating customized 3D-printed cranial implants that are tailored to the anatomy of individual animals. We performed pre-surgical computed tomography (CT) and magnetic resonance (MR) scans to generate three-dimensional

(3D) models of the skull and brain. We then used free-of-charge 3D modeling software to design implantable head posts, chambers, and a pedestal anchorage base, as well as craniotomy guides to aid us during surgery. Prototypes were made from plastic or resin, while implants were printed in titanium. The implants underwent post-processing and received a coating of osteocompatible material to promote bone integration. Results: Their tailored fit greatly facilitated surgical implantation, and eliminated the gap between the implant and the bone. To date, our implants remain robust and well-integrated with the skull. Conclusions: The use of 3D printing technology enabled us to quickly and affordably create unique, complex designs, avoiding the constraints levied by traditional production methods, thereby boosting experimental success and improving the wellbeing of the animals.

Disclosures: **X. Chen:** None. **J.K. Possel:** None. **C. Wacongne:** None. **A. van Ham:** None. **P.C. Klink:** None. **P.R. Roelfsema:** None.

Poster

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Topic: I.04. Physiological Methods

Support: This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) ElectRX program under the auspices of Dr. Doug Weber through the DARPA Contracts Management Office Contract No. HR0011-16-C-0094

Title: Neural implant insertion system using ultrasonic vibration to reduce tissue dimpling and improve insertion control and placement of penetrating microelectrode arrays

Authors: *R. S. CLEMENT, N. N. TIRKO, E. D. ASHUCKIAN, J. K. GREASER, T. J. HIGGINS, O. M. OCON-GROVE, K. N. ERDLEY, R. B. BAGWELL
Res. and Develop., Actuated Med. Inc., Bellefonte, PA

Abstract: Penetrating electrode arrays provide direct access to neural signals in central and peripheral nervous systems with high temporal-spatial resolution. Chronic electrode implants could revolutionize treatment for a range of medical conditions, including prosthetic motor control and proprioception, and brain-machine interfacing for paraplegics. However, current neural implants often fail to maintain stable, chronic multichannel neural interfaces which limit clinical translation of neural implant technology. Significant issues with neural implant performance begin with the electrode insertion procedure. Device implantation applies forces to the neural tissue resulting in significant compression (dimpling) at the implant site and strain on local tissues. Dimpling can contribute to bleeding, glial scaring, neuron death and device failure.

Additionally, tissue dimpling limits the ability to accurately target specific cortical layers and nerve fibers. To combat these challenges, we have developed a new penetrating electrode array inserter that utilizes ultrasonic vibration to improve insertion mechanics. The inserter system incorporates a piezoelectric transducer, operated in an axial resonant mode, which transmits high-frequency micro-vibrations to an attached electrode array via a reversible coupler mechanism. An integrated graphical user interface provides the user control over insertion parameters (velocity and depth), actuation details (power level, duty cycle), as well as the ability to monitor variables related to insertion kinetics. The ultrasonic inserter system has been validated for insertion of fixed microwire arrays in agar models, *ex vivo* tissues, and live rat model. Ultrasonic micro-vibration significantly reduces insertion force in agar brain models and *ex vivo* rodent brain (~78%), and tissue dimpling *in vivo* (~80%). Maximum reductions in insertion force are seen at low insertion velocities (~0.05 mm/s), permitting precise placement of electrodes in the brain. *In vivo*, arrays inserted with ultrasonic micro-vibration reliably acquire single unit activity immediately following insertion, as demonstrated in the rat barrel cortex. Ongoing studies will reveal potential improvements in chronic electrode performance and reduction in tissue damage following array insertion with ultrasonic micro-vibration. Reducing array implantation trauma and improving electrode placement is critical to maximize chronic neural interface performance, and future clinical translation of neural implant systems.

Disclosures: R.S. Clement: A. Employment/Salary (full or part-time):; Actuated Medical, Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); The Pennsylvania State University. **N.N. Tirko:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **E.D. Ashuckian:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **J.K. Greaser:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **T.J. Higgins:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **O.M. Ocon-Grove:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **K.N. Erdley:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **R.B. Bagwell:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical, Inc..

Poster

090. Electrode Arrays

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 090.26/UU34

Topic: I.04. Physiological Methods

Support: NINDS 5U01NS090557-03

MH080007

MH093807

OD010425

Simons Collaboration on the Global Brain

Title: Integration of large-scale, semi-chronic recordings of hippocampal neuronal activity in non-human primates with a wireless data acquisition system

Authors: *A. B. GOODELL[1], C. M. GRAY[1], A. LEAR[2], C. STENGEL[2], J. W. RUECKEMANN[3], Y. BROWNING[3], M. J. JUTRAS[3], E. A. BUFFALO[3]
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Abstract: To gain a greater understanding of the network mechanisms that mediate cognitive function in primates, new methods are needed to dramatically expand the ability to record ensembles of neurons throughout widespread areas of the brain. We have developed large-scale, semi-chronic recording instruments that permit the implantation of hundreds of independently movable microelectrodes in behaving non-human primates. These devices can be flexibly configured to enable the long-term measurement of neuronal activity from distributed circuits spanning the depth and breadth of the brain.
Here, we report on the design and implementation of a new system that enables long-term recording of neuronal activity from 124 independently movable microelectrodes spanning the full antero-posterior extent of the hippocampus in behaving non-human primates. We coupled the system with a 128-channel wireless data acquisition system to permit measurements during natural behaviors and periods of sleep. Using structural MRI data, we designed the chamber and microdrive so that their bottom surfaces conform to the outer and inner surfaces of the cranial bone, respectively. The system was implanted in three stages: chamber implantation, craniotomy, and microdrive implantation. Following recovery, the microelectrodes were incrementally lowered into the hippocampus over a multi-week period. Daily recordings yield neuronal activity from dozens of neurons in both the hippocampus and frontal cortex. The hippocampal electrodes sample the entire longitudinal axis simultaneously, permitting unprecedented access to network dynamics that produce fruitful yields for months.
The wireless data acquisition unit consists of four 32-channel analog front end boards for signal conditioning and digitization of input channels, a processing unit for acquisition control and command processing, a digital radio for bidirectional wireless communication, and a battery. A protective housing for the wireless system was linked to the chamber and to additional skull anchors. It was designed to be durable, compact, shield noise and provide easy daily access to change the battery and memory card.
This new approach demonstrates the feasibility of performing large-scale neuronal recordings from spatially extended structures near the ventral surface of the brain in non-human primates while they engage in natural behaviors.

Disclosures: **A.B. Goodell:** A. Employment/Salary (full or part-time):; Gray Matter Research. **C.M. Gray:** A. Employment/Salary (full or part-time):; Gray Matter Research. **A. Lear:** A. Employment/Salary (full or part-time):; Neuralynx. **C. Stengel:** A. Employment/Salary (full or

part-time):; Neuralynx. **J.W. Rueckemann:** None. **Y. Browning:** None. **M.J. Jutras:** None. **E.A. Buffalo:** None.

Poster

090. Electrode Arrays

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 090.27/UU35

Topic: I.04. Physiological Methods

Title: Investigation of role of NMDA receptor in LTP and synaptic transmission using the MED64-Quad II system on acute mouse hippocampal slices

Authors: *G. CHENG[1], S. YASUOKA[2], R. ARANT[3]
[1]Alpha Med. Scientific Inc./ Automate Scientific Inc, Berkeley, CA; [2]Alpha MED Scientific Inc, Ibaraki, Osaka, Japan; [3]Alpha MED Scientific Inc. / AutoMate Scientific Inc., Berkeley, CA

Abstract: Micro-electrode arrays (MEAs) have been widely utilized to measure neuronal activities *in vitro*. The MEA technology offers many unique advantages to investigate neuronal circuitry, interaction, models of learning and memory, development, aging, disease and neurotoxicity. While several high-throughput platforms have been utilized for drug screening with cultured cell applications in recent years, there have been limited platforms designed for acute and culture slice applications. Here we present the capabilities of the highly sensitive MED64-Quad II system, a novel medium-throughput MEA designed specifically for acute or cultured slice applications. We demonstrate the reliability and reproducibility of inducing LTP and spontaneous spike recording simultaneously in 4 acute hippocampal slices from 6-7 week old male ICR strain mice, and capability of completing experiments on 12 hippocampal slices in a day. First, I/O curves were obtained from CA1 in response to current driven stimulation delivered to the Schaffer collaterals in acute hippocampal slices heated to 32° C bath temperature. The high capacitance electrodes (55,000 pF) reliably produced greater than 1mV amplitude fEPSP at less than 30µA stimulus amplitude. The large amplitude fEPSP in response to the relatively low stimulating current is due to the low impedance of the platinum black or carbon nanotube electrodes (10 kΩ at 1 kHz). Baseline amplitude and slope of the fEPSP was recorded for 15 minutes in response to stimulating current set to 30% of the current required to saturate the fEPSP amplitude. Following theta burst stimulation, amplitude and slope were monitored for an additional 60 minutes. Pretreatment of NMDA receptor antagonist APV at 50uM in bath solution blocked LTP development. Bath application of NMDA at 10uM produced transient depression of fEPSP rather than enhancement of fEPSP. NMDA also induced synchronized burst. The synchronized burst was inhibited by APV. The results of this study indicated that the MED64-Quad II system increases throughput while maintaining high sensitivity to detect spontaneous spiking signals and long lasting fEPSP. It is a useful tool for

drug discovery, target validation, compound screening for antiepileptic drug targets and pharmacological studies in acute brain slice applications *in vitro*.

Disclosures: G. Cheng: None. **S. Yasuoka:** None. **R. Arant:** None.

Poster

090. Electrode Arrays

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 090.28/UU36

Topic: I.04. Physiological Methods

Title: Characterization of a robotic micro-surgical system for small-animal neurosurgery

Authors: N. A. NADEAU, A. CIOBANU, F. LAMER, M. COURSOLLE, S. MCBRIDE, *S. FREY, R. COMEAU
Rogue Res. Inc., Montreal, QC, Canada

Abstract: Advancements in veterinary neurosurgery have led to brain imaging and more robust planning prior to surgical intervention. Using neuronavigation software, brain imaging allows the surgeon to explore critical structures ahead of the surgery and designate targets and trajectories to target for each procedure. While brain targets may be well-defined in software, accuracy and efficiency is lost in the surgical environment due to manual human tasks and manipulation. Here we present the characterization of a robotic micro-surgical system for small-animal neurosurgery. The system is capable of moving to, drilling, injecting, placing electrodes or any other surgical device to predefined targets using imaging data and Brainsight Vet neuronavigation software (Rogue Research Inc., Montréal). Through stereo machine vision, the system is able to register a surface (e.g., exposed skull) to a given imaging dataset and calibrate an arbitrary tool in order to accurately position a 6-axis robotic arm (Mecademic, Montréal) for surgical procedures. In this particular study, we characterize the micro-surgical system using a surgical phantom in order to demonstrate the accuracy and repeatability of the tool positioning and subject registration. The experiment is designed to simulate keyhole drilling, electrode placement, and microinjections in a small-animal. The mapping between robot-space and image-space is computed using a laser-generated point cloud and stereo machine vision. Consequently, the exact placement of the animal and the alignment of bregma and lambda become irrelevant, in contrast with paper atlas stereotaxic procedures, since navigation and robot control are performed with respect to the imaging data. The robot itself is capable of 5µm repeatability, as measured with an electronic indicator (Mitutoyo 543-793). This system removes the error-prone human component from surgical procedures, allowing for a more effective and efficient surgery, with the goal of improving surgical success rate, throughput, and experiment replicability.

Disclosures: **N.A. Nadeau:** A. Employment/Salary (full or part-time):; Rogue Research Inc. **A. Ciobanu:** A. Employment/Salary (full or part-time):; Rogue Research Inc. **F. Lamer:** A. Employment/Salary (full or part-time):; Rogue Research Inc. **M. Coursolle:** A. Employment/Salary (full or part-time):; Rogue Research Inc. **S. McBride:** A. Employment/Salary (full or part-time):; Rogue Research Inc. **S. Frey:** A. Employment/Salary (full or part-time):; Rogue Research Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rogue Research Inc. **R. Comeau:** A. Employment/Salary (full or part-time):; Rogue Research Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rogue Research Inc.

Poster

090. Electrode Arrays

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 090.29/UU37

Topic: I.04. Physiological Methods

Support: NINDS (1U01NS094375-01)

Title: Implantation analysis of a 16-channel carbon fiber microelectrode

Authors: *C. M. CALDWELL[1], D. ROOSSIEN[2], P. R. PATEL[3], P. POPOV[4], E. J. WELLE[5], D. EGERT[6], J. D. BERKE[7], D. CAI[2], C. A. CHESTEK[3]
[1]Biomed. Engin., Ann Arbor, MI; [2]Cell and Developmental Biol., [3]Biomed. Engin., [4]Psychology, [6]Electrical Engin. and Computer Sci., [5]Univ. of Michigan, Ann Arbor, MI; [7]UCSF, San Francisco, CA

Abstract: Histological analysis of neural circuitry surrounding implantable intracortical microelectrodes is critical for neuroscience research. Unlike other microelectrodes, carbon fiber (CF) microelectrodes minimally damage the neuronal cell density and are small enough to be left in the brain during slicing (Kozai 2012). We took advantage of this capability to slice and stain a complete multielectrode array in the transverse plane after chronic implantation.
A 16-channel CF array (8 fibers/row) was implanted in a Long Evans rat in the nucleus accumbens for 82 days using a glass cannula to implant at a depth of 8.5 mm from the skull surface. The array pitch was 132 µm, row spacing was 50 µm, and PCB length was 1 cm. CFs had a diameter of 8.4 µm and length of 500 µm (N=15, 1 broken before implant). 100% of CFs implanted successfully. After sacrifice, the tissue surrounding the skull was removed, the skull was decalcified in EDTA (~4 weeks), and 300 µm thick brain slices were collected by slicing in the transverse plane. Nissl was used to stain for neuronal bodies. The brain slice containing the tips was imaged with a confocal microscope using 40x magnification.
A MATLAB script (I.N.T.E.N.S.I.T.Y. Analyzer) was used to perform intensity-based radial

analysis of the Nissl stain (Kozai 2014). Three equally spaced images from the tips to the uppermost image were analyzed. Only holes that were spaced at least 40 µm apart were used in neuron density calculations (N=8). Average gray scale intensity for all pixels above the background noise intensity threshold was calculated and normalized to the background. Welch's two-sample t-test with a *p*-value of 0.05 was used compare intensity values between 25 µm and 75 µm (*p*-value = 0.001358) and 75 µm and 125 µm (*p*-value = 0.6819).
In the images, the CF array was identified by a visible fiber or distinct hole created in the tissue in the original 16-channel configuration. The average hole diameter was 8.5 ± 1.8 µm (N = 635 measurements), which is comparable to the original fiber diameter of 8.4 µm. The average pitch between holes was 121.9 ± 13.8 µm (N = 798 measurements), indicating minimal movement of fibers during insertion. The average normalized intensity for a radius less than 100 µm from each hole was 1.13 ± 0.06, indicating neuron intensity surrounding the holes is slightly higher than the background, which appears to be due to neurons clustering around the electrode. Going from 25 µm and 75 µm there was a small, yet significant increase in intensity of 5.44% and no significant difference between 75 µm and 125 µm.
Similar images will be used in future analyses in conjunction with electrophysiological recordings.

Disclosures: C.M. Caldwell: None. **D. Roossien:** None. **P.R. Patel:** None. **P. Popov:** None. **E.J. Welle:** None. **D. Egert:** None. **J.D. Berke:** None. **D. Cai:** None. **C.A. Chestek:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.01/UU38

Topic: I.06. Computation, Modeling, and Simulation

Title: Finite element model of the transmembrane voltage of axon during kilohertz frequency alternating current stimulation for nerve conduction blockage

Authors: *A. GHAZAVI, S. COGAN
Bioengineering, Univ. of Texas At Dallas, Dallas, TX

Abstract: Kilohertz frequency alternating currents (KHFAC) have been used extensively in animal studies as a tool for blocking nerve conduction (Kilgore and Bhadra, 2014) and, recently, high frequency stimulation has been employed in clinical trials for treating obesity (Camilleri *et al.*, 2008), chronic back pain (Tiede *et al.*, 2013) and post-amputation pain (Soin *et al.*, 2015). The sinusoidal current waveforms employed in KHFAC stimulation can be differentiated from low repetition rate pulsatile electrical stimulation used to excite neural activity by the absence of a period between pulses in which the transmembrane potential is not actively controlled. In many

previous modeling studies of axonal activation the electrode has been considered as a point source (Kilgore *et al.*, 2004) and thus the effect of nonuniform current density distribution at the electrode on transmembrane potential of the nerve is ignored. In this study, the effect of high frequency stimulation on current density distribution on the electrode surface has been evaluated. To model the primary current density distribution at the electrode-electrolyte interface, COMSOL v5.2 (COMSOL Inc., USA) a finite element modeling (FEM) software package was used. A transient axisymmetric FEM was developed to simulate the electrode interface in two dimensions. The model includes three domains; electrode, insulator, and electrolyte. The model was solved for Laplace's equation for both the electrode and electrolyte domains. Conservation of current and Ohm's law were solved for the electrode and electrolyte domains. The boundary conditions applied to this model were: V = 0 at the external boundaries of electrolyte domain, I = Asin (2πft); A=3 mA, f=50 kHz at the electrode, $V_{electrode}$-$V_{electrolyte}$ = $E_{equilibrium}$ at the electrode-electrolyte interface where $V_{electrode}$ is the electrode potential, $V_{electrolyte}$ the electrolyte potential, $E_{equilibrium}$ electrode's equilibrium potential, and n□J = 0 at the insulator where n is the normal vector. The model is composed of 57820 free triangular mesh elements. The model was verified by comparing experimentally measured voltage transients at an electrode with model predictions, which yielded a 6% difference. The modeling results revealed a high nonuniformity of the current density distribution across the electrode surface. To achieve a better understanding of the effect of the nonuniform current density distribution on the transmembrane potential, a nerve axon has been included in the model. This model can provide us a better understanding of the nerve conduction block mechanism and the safety of KHFAC with respect to blocking-induced nerve damage.

Disclosures: **A. Ghazavi:** None. **S. Cogan:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.02/UU39

Topic: I.06. Computation, Modeling, and Simulation

Support: MEXT KAKENHI Grant Number 16H01527

JSPS KAKENHI Grant Number 15K00391

Title: Reduction of the dynamics of a stochastic neuronal model by using non-negative matrix factorization

Authors: *T. YAMANOBE
Hokkaido University, Sch. of Med., Sapporo, Hokkaido, Japan

Abstract: In this study, we aimed to reduce the linear operator that describes the dynamics of a neuronal model by using non-negative matrix factorization with a sparseness constraint and to extract the mathematical structure in the neuronal model. The neural network theory states that the information carrier in the artificial neural network model depends on the “output function” of each element. Furthermore, several studies have suggested that spikes are generated in the transient regime. Neurons also have several sources of noise, such as ion channel and synaptic noises. For elucidating information carriers in the nervous system, the “output function” should be identified, which considers the transient dynamics and neuronal noise. Therefore, the dynamics of stochastic neuronal models in the whole phase space should be investigated. Hence, we derived a linear operator that describes the statistical global behavior of the neuronal model receiving a time-varying pulse train [1, 2]. Although this linear operator is theoretically shown to be approximated by a matrix of finite dimensions, the dimension of the simple discrete approximation of the linear operator becomes high, which makes analysis of the statistical global behavior of the given neuronal model difficult. Therefore, we reduced the linear operator by using non-negative matrix factorization. The linear operators that describe the statistical global behavior of stochastic neuronal models are sparse. Furthermore, this linear operator has parameters that determine the input pulse train to the stochastic neuron model and the state of the neuronal model. The input parameters change with time; hence, the linear operators for each set of parameter values must be reduced to investigate the properties of the corresponding linear operator. We use a non-negative matrix factorization with sparseness constraints [3]. This method allows us to make a set of basis functions by using the given kernel function of the linear operator and the coefficient that describes the contribution of each basis function. We examined whether non-negative matrix factorization can approximate the kernel of the linear operator and showed that the kernel of the linear operator can be reproduced by using the set of basis functions and the corresponding coefficients.
[1] T. Yamanobe, Phys. Rev. E., Vol. 84, 011924 (2011).
[2] T. Yamanobe, Phys. Rev. E., Vol. 88, 052709 (2013).
[3] P. O. Hoyer, Journal of Machine Learning Research, Vol. 5, 1457-1469, (2004).

Disclosures: T. Yamanobe: None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.03/UU40

Topic: I.06. Computation, Modeling, and Simulation

Title: In-silico sythesis of structural perivascular astrocytic endfeet

Authors: E. ZISIS, *D. KELLER, H. MARKRAM
Blue Brain Project, Brain Mind Institute, EPFL, Lausanne, Switzerland

Abstract: The chemotropic mechanisms that underlie astrocyte polarization by secreted cues from vascular endothelial cells are still to this day elusive, given the coupled spatial and temporal bidirectional interaction between angiogenesis and gliogenesis. However, the end result of this process is that mature astrocytes have been observed to minimize the diffusional path length between the vasculature and their tripartite connections for the optimization of nutritional support. Using this result, we algorithmically generated the geometry of the astrocytic perivascular endfeet using digital reconstructions of neocortical vasculature datasets and the statistics extracted from a small number of EM astrocyte morphologies. As a result, we were able to generate a gliovascular circuit, i.e. the astrocytes, the vasculature network and their pairwise connections. We distributed astrocyte somata in a rectangular space to match the average cell densities in the rat neocortex and their nearest neighbor distributions, co-localized with the reconstruction of the neocortical vasculature. Next, we used stochastic growth algorithms for the generation and attachment of perivascular endfeet to the vascular surface, and we evaluated the validity of our in silico model against literature sources. Finally, we varied the spatial pattern of astrocytic somata and generated multiple endfeet in order to address the following unresolved question: what is the importance of the astrocyte positioning for the trophic support they can provide in their anatomical microdomains?

Disclosures: E. Zisis: None. **D. Keller:** None. **H. Markram:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.04/UU41

Topic: I.06. Computation, Modeling, and Simulation

Title: A NetLogo model of the Notch regulatory network in the determination of neural patterning

Authors: *E. R. REYNOLDS[1], A. LUTZ[1], J. PFAFFMANN[2]
[1]Program in Neurosci., [2]Computer Sci., Lafayette Col., Easton, PA

Abstract: The Notch signaling pathway is involved in cell fate decision and developmental patterning in diverse organisms. We have created an agent-based model that simulates the molecular components of this pathway acting within a cellular spatial representation to explore the formation of a larger pattern within a multicellular system. Agent-Based Modeling (ABM) allows for a representation of these individual components within a system and our model captures how the levels of these components are regulated, their transition from one state to

another, and their movement from the nucleus to the cell membrane and back. Most steps introduce randomness into the system using probabilities of events rather than sequential direct implementation. The model then has 3 levels of complexity-the specific timing and level of each molecular component within each cell, the interactions between cells, and the formation of pattern across the system. For a broad set of parameters, the current model accurately reproduces the rosette pattern of neurons and skin cells in the system through oscillations in cell fate that settle into the pattern. We manipulated several parameters to examine their effect on cell fate as well as system pattern. We found that the timing and the availability of the Notch components of the system were central to the formation of a correct and stable pattern. However, the Delta components, that represent the Notch receptor, were also crucial in that there was a necessary balance with the Notch components to produce proper cell fate and system pattern.
Currently we are exploring the consistent dynamics and rule set for the formation of the pattern within the model. Although the larger pattern fluctuates as it develops over time, the edges of the field are important in driving that pattern. These cells have a set of directional interactions with a more limited number of surrounding cells, which allow their individual state to stabilize and impact the fate of surrounding cells. The rule set is being adapted to conceptualize the model in terms of a cellular automaton allowing for rule exploration that can be confirmed in the more detailed model.

Disclosures: **E.R. Reynolds:** None. **A. Lutz:** None. **J. Pfaffmann:** None.

Poster

091. Modeling

Location: Halls A-C

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Topic: I.06. Computation, Modeling, and Simulation

Support: Univ. Sussex School of Life Sciences PhD studentship

EPSRC grant EP/P006094/1

EU-H2020, Human Brain Project

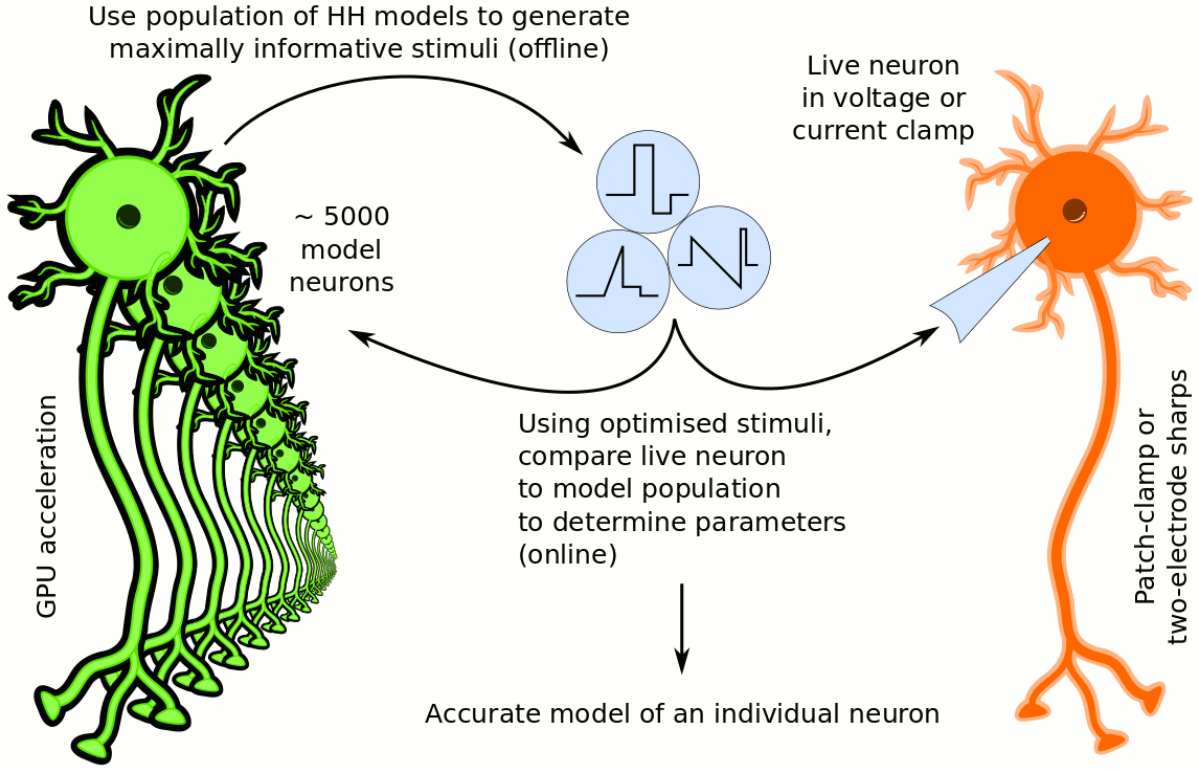
HFSP grant RGP0053/2015

Title: Implementing a dynamic observer strategy to rapidly fit single-cell models to live neurons

Authors: *F. B. KERN, T. NOWOTNY, G. KEMENES
Sussex Neurosci., Univ. of Sussex, Brighton, United Kingdom

Abstract: Most currently available methods of constructing conductance-based biophysical models of neuronal activity are not suitable for finding valid descriptions of individual neurons.

Instead, models are fitted to average data and individual variability is discarded. In addition, there are no methods for tracking the changes of neuronal properties over time induced e.g. by intrinsic plasticity, cellular homoeostasis, or the extrinsic modulation of ion channels.
Here, we present first steps towards addressing these shortcomings. We have developed a method to rapidly and accurately fit a Hodgkin-Huxley-type model to a live neuron. To achieve this, we use a set of algorithmically designed stimulus patterns, specific to the assumed model equations, to separate the influences of individual parameters.
We show that our method of model fitting performs well in simulation and present evidence of its successful use in a live system. As our fitting algorithm arrives at a stable model within mere minutes, we can verify the resulting model in the still living neuron. Using this feature, we present evidence that our method yields an accurate model of the target neuron.



Disclosures: **F.B. Kern:** None. **T. Nowotny:** None. **G. Kemenes:** None.

Poster

091. Modeling

Location: Halls A-C

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Topic: I.06. Computation, Modeling, and Simulation

Support: European Union's Horizon 2020 (agreement No. 720270)

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UK-BBSRC/MRC grant: BB/F529254/1

ErasmusMundus EuroSPIN

Title: Meta-analysis of biophysical models of synaptic plasticity and the overlap of modelled elements with the synaptic proteome

Authors: *K. F. HEIL, E. WYSOCKA, O. SOROKINA, T. I. SIMPSON, J. D. ARMSTRONG, D. C. STERRATT
Univ. of Edinburgh, Sch. of Informatics, Edinburgh, United Kingdom

Abstract: Consistent with the crucial role of synapses in neuronal communication and experience-dependent plasticity, disruptions to genes for synaptic proteins affect synaptic plasticity, and underlie diseases such as schizophrenia, depression and Parkinson's Disease. Since the late 1980s, a range of dynamical models of different aspects of synapses and underlying molecular reactions have been published.
We identify the set of ions, receptors and proteins involved in each of 28 computational models of synapses. Models sometimes specify elements at the level of a protein family, and do not always specify the subunit composition of receptors, so we developed a mapping of model elements onto proteins. This allowed us to construct the set of proteins potentially in each model, and therefore the set of all 359 proteins potentially in models. Of these, 281 proteins are to be found in the set of 6706 proteins proteomic assays imply to be in synapses (the synaptic proteome), suggesting that a number of important proteins have not yet been included in models. The number of modelled postsynaptic proteins is higher than the number of modelled presynaptic proteins, nevertheless a higher percentage of the presynaptic proteome has been modelled. Initial signalling pathways are highly modelled, in particular Ca-CaM-CaMKII and Ca-calcineurin-I1/DARPP-32-PP1-CaMKII.
Functional and disease enrichment of the modelled proteins shows that modelled proteins are enriched in functions such as calmodulin binding, cellular responses to glucagon stimulus, G-alpha signalling and DARPP-32 events. Schizophrenia and Alzheimer's Disease are two of the enriched diseases. A small set of proteins that are crucial to a selected set of neurological disease are highly modelled (CACNA1C, DRD2) whereas others have not been included in models (COMT, SLC6A3).
In addition to these findings, we have made our catalogue of components in models available as an online resource, allowing models to be queried by component. The catalogue of models allows us to cluster models according to the similarity of their elements, making clear various classes of model.
We consider how models in the computational neuroscience field can be developed to address the challenges of including more detailed bioinformatics data and a wider range of proteins.

Disclosures: K.F. Heil: None. **E. Wysocka:** None. **O. Sorokina:** None. **T.I. Simpson:** None. **J.D. Armstrong:** None. **D.C. Sterratt:** None.

Poster

091. Modeling

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Program#/Poster#: 091.07/UU44

Topic: I.06. Computation, Modeling, and Simulation

Support: Canadian Institutes of Health Research

Title: A Hodgkin-Huxley type model of subfornical organ neurons

Authors: *L. MEDLOCK[1], W. M. FRY[2], D. STANDAGE[1], A. V. FERGUSON[1]
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Abstract: The subfornical organ (SFO), a circumventricular organ that lacks the blood brain barrier (BBB), plays an important role in sensing various blood-borne signals from the peripheral circulation. SFO neurons integrate these signals and transmit them across the BBB to regulate critical autonomic functions, including cardiovascular and energy homeostasis. Previous findings from *in vitro* studies have established that SFO neurons exhibit a heterogeneity in their expression of ionic currents and consequent spiking behaviour, as well as their response to circulating peptides. Insight into the mechanisms behind this heterogeneity is critical for understanding how the SFO integrates and regulates autonomic function, but is currently lacking due to the limitations of patch-clamp techniques. To address this limitation, we developed a Hodgkin-Huxley style (HH) model of an SFO neuron, searching biophysical parameter values to match *in vitro* spike train data. The resulting HH model demonstrated the two major spiking behaviours exhibited by SFO neurons: tonic firing and bursting, where bursting is characterized by robust membrane potential bistability. These spiking behaviours were produced under different parameter values for a non-selective cation current, transient potassium current, persistent sodium current, and current noise. Established methods for neuronal spike train analysis were then used to classify SFO neurons based on their spiking behaviour, e.g. the coefficient of variation and distribution of interspike intervals, as well as their membrane potentials. Analysis of membrane dynamics characterized the neuronal mechanisms supporting these spiking regimes. These methods were further used to predict the behaviour of SFO neurons in response to the binding of angiotensin-II (ANG), a peptide hormone that acts within the SFO to influence various functions including blood pressure and fluid balance. Future use of this model will allow us to study the integration of ANG and other autonomic signals within the SFO.

Disclosures: L. Medlock: None. **W.M. Fry:** None. **D. Standage:** None. **A.V. Ferguson:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.08/UU45

Topic: I.06. Computation, Modeling, and Simulation

Support: CHDI

Title: The role of calcium microdomains in modifying synaptic efficacy via gain control of electrical propagation through MSN spines and dendrites

Authors: *T. M. HOANG TRONG, T. H. RUMBELL, J. KOZLOSKI
IBM Res., Yorktown Heights, NY

Abstract: Microdomains of calcium are important in regulating local cellular signals. One type of microdomain couples the plasma membrane and membrane of the endoplasmic reticulum (ER) and is formed by the support of junctophilin. Local elevation of calcium is higher in microdomains and enhances through calcium-induced calcium release (CICR) the gating of intracellular calcium channels known as ryanodine receptors [Verkhratsky, Shmigol, 1996]. In dopaminergic neurons, microdomains are important in regulating firing patterns [Cui, Okamoto, Morikawa, 2004]. Another form of microdomain is the coupling of the protein complexes Kv4.2-KChIP-Cav3 [Anderson et al., 2010]. This coupling is important in regulating the effectiveness of back-propagating action potential (bAP) and precise timing of neuronal hyperpolarization following depolarization due to the very local effect of Ca^{2+}. This is suggested to link to the differential excitability found between D1- and D2-MSN neurons [Day et al., 2008]. Huntington's disease (HD) is an autosomal dominant neurodegenerative disease that causes a hallmark in striatal degeneration. In Huntington's Disease mouse model of early symptomatic HD, failing of TrkB receptors to engage in the postsynaptic signaling for corticostriatal synapses [Plotkin et al., 2014] and there are evidences that the downstream effect of TrkB receptor signaling link to KChiP. We introduce a novel computational system to link microdomain model to the level of an entire cellular model and relate the model to observations found in Huntington's Disease.

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Plotkin, J. L.; Michelle Day; ⋯; D. James Surmeier; "*Impaired TrkB Receptor Signaling Underlies Corticostriatal Dysfunction in Huntington's Disease*", Neuron (2014), 83, 178-188

Disclosures: T.M. Hoang Trong: None. **T.H. Rumbell:** None. **J. Kozloski:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.09/UU46

Topic: I.06. Computation, Modeling, and Simulation

Support: This work was funded by the Okinawa Institute of Science and Technology Graduate University.

The work was supported by the EPFL Blue Brain Project Fund, ETH Board funding to the Blue Brain Project and European Union Seventh Framework Program (FP7/2007-2013) under grant agreement no. 604102 (HBP).

Title: Whole cell 3D stochastic molecular simulation with STEPS

Authors: *E. DE SCHUTTER[1], I. HEPBURN[1], W. CHEN[1], F. CASALEGNO[2], A. DEVRESSE[2], F. PEREIRA[2], F. DELALONDRE[2]
[1]Okinawa Inst. of Sci. and Technol., Onna-Son, Japan; [2]Ecole Federale Polytechnique de Lausanne, Geneva, Switzerland

Abstract: The field of computational neuroscience has adopted a standard approach to represent real neurons digitally, which is to apply a cable-like description of cellular morphology coupled with ODE descriptions of ion channels. The time evolution of the system is then usually deterministically simulated, often in a standard tool such as NEURON. Due to the relative computational simplicity of the approach it has been the only feasible way to describe morphological neurons and study their behavior on available hardware to date, an approach that has played an important role in advancing our understanding of neuronal behavior in the past two decades, complementary to experimental studies.
Advancing computational power and improving understanding of complex neuronal makeup have led to an increased focus on stochastic neuronal simulation in recent years. In this approach, the ion channels and other molecular components of the cell are represented to sub micrometer resolution and their interactions solved stochastically - an approach that aims to capture the inherent uncertainty in such systems.
Digital reconstruction techniques have advanced to a point where neuronal morphology can be

recorded to high detail and represented by surface or volumetric meshes with high accuracy. Stochastic simulator STEPS (homepage: steps.sourceforge.net, public release repository: github.com/CNS-OIST/STEPS) supports tetrahedral meshes and so maintains high spatial realism from real neurons, and also employs high molecular realism where the biochemical and electrophysiological behavior of the cell are closely coupled. These simulations can elicit interesting features of such systems that are absent from deterministic approaches.
Stochastic simulation is computationally intensive and standard techniques are serial in nature, which has to date rendered the method limited in scale to e.g. small, isolated regions such as spines, and has rarely been extended to the whole cell scale due to runtime concerns. This has forced research into parallel methods, which is a promising direction for the field due to the increasing availability of supercomputers to researchers.
We developed an inherently parallel reaction-diffusion method that did not sacrifice simulation accuracy and coupled it with a voltage calculation using an iterative solver that could scale well up to hundreds of computer cores. We report on performance and scalability of our methods, and describe a realistic stochastic simulation of Purkinje cell excitation on the whole-cell scale where interesting features have emerged from the stochastic system that are absent when deterministic modeling techniques are applied.

Disclosures: **E. De Schutter:** None. **I. Hepburn:** None. **W. Chen:** None. **F. Casalegno:** None. **A. Devresse:** None. **F. Pereira:** None. **F. Delalondre:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.10/UU47

Topic: I.06. Computation, Modeling, and Simulation

Support: Swedish Research Council, Project 22209

CIHR 353197

Title: Data-driven spiking models for computations of first-order tactile neurons in human fingertips

Authors: *E. HAY, A. PRUSZYNSKI
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Abstract: Recent studies in various modalities indicate that peripheral sensory neurons (e.g. retinal ganglion cells) have computational capabilities often attributed to neurons in the cerebral cortex. Our own work in this respect has focused on two types of first-order tactile neurons

innervating the human fingertips: fast-adapting type 1 (FA-1) neurons innervating Meissner corpuscles and slow-adapting type 1 (SA-1) neurons innervating Merkel cells. We have recently shown that both types of neurons have complex receptive fields and are able to perform computations such as detection of edge-orientation and geometric feature extraction. While we have previously demonstrated that the computations of a first-order tactile neuron can be estimated to a fair degree via linear integration of the stimulus by the complex receptive field as inferred from dot stimuli, spiking/nonlinear models that better estimate the underlying physiology and more accurately reproduce the responses are lacking. Here, we utilized data of spike recordings from human first-order tactile neurons in response to a variety of behaviorally-relevant stimuli such as dots and edges. We derived spiking models using genetic algorithm to find model weights at each patch of the receptive field grid which best reproduced the multiple observed spike patterns. We show that this method yields models that fit the spiking data with high accuracy, and we simulated model response to novel stimuli to further elucidate the coding of tactile stimuli in human fingertips by single neurons and neuronal populations.

Disclosures: **E. Hay:** None. **A. Pruszynski:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.11/UU48

Topic: I.06. Computation, Modeling, and Simulation

Title: Identifying functional regulatory units controlling dopamine neuron subthreshold oscillation properties using a population-based approach to parameter optimization

Authors: *T. RUMBELL[1], J. KOZLOSKI[2]
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Abstract: Dopaminergic neurons of the substantia nigra pars compacta can display large amplitude subthreshold oscillations in vitro under blockade of spike-generating mechanisms. These oscillations result from the interplay of several low-voltage activated ion channels. However, electrophysiological experiments have demonstrated substantial variability in currents produced by these channels as well as the gating properties of the channels themselves (Amendola et al., 2012), suggesting multiple ways that these membrane characteristics are produced. We used a novel, population-based evolutionary algorithm to simultaneously tune 22 parameters from 7 subthreshold ion channels and the intracellular calcium mechanism, generating many candidate models covering the range of observed subthreshold oscillation behaviors. Through dimensionality-reducing analytical techniques, we identified linear combinations of parameters, which we term functional regulatory units, that are capable of

independently controlling subthreshold oscillation amplitude and frequency. We simulated application of apamin, blocking the calcium-dependent potassium channel, and found that models with parameter sets in line with the functional regulatory units produce consistent and reliable responses to the drug, whereas models generating their behavior using parameter combinations that are inconsistent with the functional regulatory units produce less predictable responses to the drug. These new techniques have broad implications for simulating populations of neurons, understanding ion channel combinations controlling neural behavior, drug discovery, and neurodegenerative disease.

Disclosures: **T. Rumbell:** None. **J. Kozloski:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.12/UU49

Topic: B.07. Synaptic Transmission

Support: NSF grant # 1557474 to JSH

Lehigh CAS Undergraduate Research Grant to TAP

Whitehall Foundation to JSH

Title: A computational model of electrical synapse function within the thalamocortical relay circuit

Authors: *T. PHAM, J. S. HAAS
Dept. of Biol. Sci., Lehigh Univ., Bethlehem, PA

Abstract: The thalamic reticular nucleus (TRN) regulates thalamocortical (TC) activity during the process of sensory relay to cortical neurons, through feedback GABAergic inhibition from TRN neurons to TC neurons and through electrical synapses between TRN neurons. Previous computational studies have focused mainly on synchrony of rhythmic activity involving both TC and TRN neurons, while the implications for specific sensory-evoked responses in the network are underexplored. Through computational modelling, we explore the varying effects of electrical synapses and inhibition mediated by TRN on the timing of evoked responses in TC neurons.
We based our model on pairs of single-compartment Hodgkin-Huxley TRN and TC neurons. Each TRN-TC pair forms a closed loop as an excitatory-inhibitory pair, and we coupled two TRN-TC pairs by a single ohmic electrical synapse between the TRN neurons. The TC neuron of one pair receives a single evoked synaptic input with a fixed time and amplitude, while the TC neuron of the other pair receives a similar input but with varying arrival times and strengths. To

characterize the behavior of our model network, we quantified spiking rate, and temporal independence of the TC neurons as the duration of the active spiking window in one TC neuron that does not overlap with the other TC neuron. Higher independence of TC neuron spiking offers a target cortical neuron a better chance to differentiate the inputs it receives from thalamus.
Our model shows that, acting through feedback inhibition, electrical synapse strength affects both spiking rate and independence of TC neurons. As expected, TC spiking rates decrease with stronger electrical synapses. Inputs that arrive to the TC cells with disparate timing or with different strengths become more easily separable when both sufficient inhibition and electrical synapse strength cause either truncation, delay or termination of TC spiking.
Our work demonstrates a set of mechanisms by which both gap junction between and feedback inhibition from TRN neurons interplay to help cortical neurons separate different sensory input streams arising from thalamus, although sometimes at the cost of diminished spiking rate. We plan to integrate crosstalk inhibition between the two TRN-TC pairs to study how sensory information can be further regulated by lateral inhibition from TRN neurons of different receptive fields.

Disclosures: T. Pham: None. **J.S. Haas:** None.

Poster

091. Modeling

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 091.13/UU50

Topic: E.05. Brain-Machine Interface

Support: NIH Grant NS095123

Title: Direct current stimulation and synaptic plasticity: The role of endogenous synaptic activity and membrane polarization

Authors: *G. KRONBERG, A. RAHMAN, M. BIKSON, L. C. PARRA
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Abstract: Transcranial direct current stimulation (tDCS) has recently received attention for its ability to modulate brain function and potentially improve treatments for brain disorders. To date, little is known about how the effects of stimulation at the cellular level translate into changes in cognitive function, particularly long-term changes that outlast stimulation. A common hypothesis is that tDCS alters synaptic plasticity. Indeed, DCS can modulate synaptic plasticity in brain slices and studies in humans have demonstrated effects that resemble canonical synaptic plasticity. Acutely, during stimulation, tDCS is also known to modulate various measures of function in individual neurons and networks (e.g. presynaptic release probability, synaptic

integration, excitability, oscillatory activity). It is presumably these acute effects that are translated into long-term changes in synaptic plasticity once stimulation has ended. A major obstacle to predicting plasticity outcomes is that even within a single tDCS paradigm (i.e. electric current location, direction, and magnitude), there is a tremendous space of potential acute effects, depending on the orientation of neuronal subcompartments (soma, axon, dendrites) and their activity states during stimulation (including their recent history). There is also likely to be a large space of plasticity outcomes as a function these acute effects, some of which we demonstrate here. We explore how DCS modulates synaptic plasticity in response to varying orientation of neuronal subcompartments and synaptic activity patterns. We propose a framework for making specific predictions about how DCS will modulate synaptic plasticity as a function of these parameters.

Disclosures: **G. Kronberg:** None. **A. Rahman:** None. **M. Bikson:** None. **L.C. Parra:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.01/UU51

Topic: I.06. Computation, Modeling, and Simulation

Support: Swedish Research Council within the UPMARC Linnaeus center of Excellence

Title: Multiscale modelling of spiking activity via split-step methods

Authors: ***P. BAUER**[1], S. MIKULOVIC[3], A. SENEK[2], S. ENGBLOM[2]
[1]Information Technol., [2]Uppsala Univ., Uppsala, Sweden; [3]Uppsala University, Neurosci. Dept., Uppsala, Sweden

Abstract: Neuronal models based on the Hodgkin-Huxley equation form a fundamental framework in the field of computational neuroscience. While the neuronal activity is often modelled deterministically, experimental recordings show stochastic fluctuations, presumably driven by molecular noise from the underlying microphysical conditions. In turn, the firing of individual neurons gives rise to an electric field in extracellular space.
We develop a multiscale model which combines a stochastic ion channel gating process taking place on the neuronal membrane, together with the propagation of an action potential along the neuronal fibre. We devise a numerical method relying on a split-step strategy which effectively couples these two processes and we experimentally test the feasibility of this approach. Importantly, we show how the choice of split step size affects the distribution of inter-spike-intervals in the solution. Finally, we explain how the approach can be extended with Maxwell's equations to allow the potential to be propagated in extracellular space. The software used in the study is built around URDME, a modular simulator for reaction and diffusion processes.

Disclosures: **P. Bauer:** None. **S. Mikulovic:** None. **A. Senek:** None. **S. Engblom:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.02/UU52

Topic: I.06. Computation, Modeling, and Simulation

Support: Swartz Foundation

Title: Gamma rhythms depend upon, and influence, firing rates and spike-timing in a computational model of cerebral cortex

Authors: *C. L. CHARIKER[1], R. M. SHAPLEY[3], L.-S. YOUNG[2]
[1]Mathematics, New York Univ., Brooklyn, NY; [2]Mathematics, New York Univ., New York, NY; [3]Ctr. for Neural Sci., New York, NY

Abstract: Our aim is to understand the dynamical mechanisms for the generation and processing of spike-timing information in cerebral cortex. Towards this aim, we have studied gamma rhythms, which have been shown to carry stimulus information. How gamma is produced is not yet completely known. Furthermore, the dynamical effects gamma rhythms have on population activity also are not well understood. We investigated (1) what neurobiological factors lead to the generation and shaping of gamma rhythms, and (2) which features of synchronous spiking activity in feedforward/feedback input have an effect on local population activity. To tackle these questions, we used a comprehensive, data-driven, computational model of macaque V1 described in (Chariker et. al. JNS 2016). The model is composed of O(10,000) integrate and fire excitatory (E) and inhibitory (I) cells, covering several hypercolumns in the V1 input layer 4Cα. Model cells are conductance-based, simulating AMPA, GABA, and NMDA receptors, and the network is driven by sparse LGN feedforward input, as well as feedback input from other layers. This model is ideal for answering questions (1) and (2): the model is of a specific part of the brain where gamma rhythm occurs, and where plenty of neuroanatomical data is available; the model simulates the dynamical activity of local populations of neurons, generating emergent, robust gamma band fluctuations when stimulus-driven; and the model simultaneously produces several different visual functions of V1. To answer (1), the model shows that competition between E and I populations generates gamma fluctuations; and anatomical and biophysical factors that shift the balance in favor of either E or I shape gamma. Also, the rise and decay times of EPSC and IPSC time-courses strongly influence the frequency, size, and duration of gamma. To answer (2), we generate from our model several sets of spike trains differing in amount and shape of gamma activity, and we supply each such spike train as feedforward input to a second simulated cortical layer. This scheme allows us to estimate the effects of gamma band synchronization on local population firing rates and spike timing. In addition to examining population activity, we also

look at single neuron dynamics of model cells in various regimes of local oscillatory activity. We find both in the single neuron and local population cases that, with feedforward firing rate held fixed, varying degrees of synchronization can have a strong influence on spike rate and spike-timing in the second layer. Incoming spike-timing information matters very much for the behavior of a single neuron or a local population of neurons in our realistic computational model.

Disclosures: C.L. Chariker: None. **R.M. Shapley:** None. **L. Young:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.03/UU53

Topic: I.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI Grant 15K06715

Title: Heterogeneous layers stabilize propagation of a spike signal in a feedforward network

Authors: *S. HONG[1], D. HAN[2], E. DE SCHUTTER[3]
[1]Okinawa Inst. of Sci. and Technol., Okinawa, Japan; [2]Okinawa Inst. of Sci. and Technol., Onna-son, Japan; [3]Okinawa Inst. of Sci. and Technol., Onna-Son, Japan

Abstract: Feedforward networks are ubiquitous structures in neural systems and have been studied in many contexts, such as models for signal transmission (Kumar et al., Nat Rev Neurosci, 2010), architectures for rich information processing (Serre et al., PNAS, 2007), etc. However, studies have ignored an important property often observed in real feedforward networks: neurons in one layer have contrasting characteristics from those in other layers. For example, the cerebellar granule cells are tiny and relatively simplistic neurons while their postsynaptic targets, the Purkinje cells, are much bigger, complex, and therefore have very different intrinsic properties. What would be the role of such layer-to-layer differences in neural circuits?
Here we address this question by simulation of a model feedforward network, inspired by a recent experimental study on the Drosophila olfactory system (Jeanne and Wilson, Neuron, 2015). In this model, all the adjacent layers have Morris-Lecar neurons with different excitability types from each other and therefore different computational functions. If one layer has cells with class I excitability, which behave like integrators of inputs, neurons in their postsynaptic layer are of class III, which act as coincidence detectors (Ratté et al, Neuron, 2015), and vice versa. We found that spikes from one layer evoked a response in next layer neurons better when they had the same excitability type. However, in a deep feedforward network, this caused gradual accumulation of signal distortion, leading to the undesirable responses in deep layers that all the neurons either fired synchronously or became silent, as seen in classical studies. On the other

hand, the network with heterogeneous layers showed stable propagation of a signal into deep layers with a preserved temporal fidelity and spike count. We analyzed the result and demonstrated that this feature is due to a novel signal transformation property arising from mixing layers with different coding schemes, seen in the Drosophila olfactory system (Jeanne and Wilson, Neuron, 2015). We conclude that heterogeneous layers in feedforward neural networks can be a mechanism for optimal information transfer.

Disclosures: S. Hong: None. **D. Han:** None. **E. De Schutter:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.04/UU54

Topic: I.06. Computation, Modeling, and Simulation

Title: Macroscopic phase resetting-curve for spiking neural netwoks: Theory and application

Authors: *G. D. DUMONT, ESQ, B. GUTKIN
Ecole Normale Superieure, Paris, France

Abstract: The study of brain rhythms is one of the most challenging subjects of interest in neuroscience. An understanding of their functional implications and computational roles could be facilitated by the use of phase resetting curve (PRC); a powerful analytical tool in use to study rhythms. However, the topic of PRC for global oscillations observed at the macroscopic scale in neural circuits has received little attention so far. The reason is that macroscopic rhythms emerge from the synaptic interaction of thousands of spiking cells. Although we look at the network as an oscillator and define its phase cycle in term of ongoing self-sustained rhythmic activity, it is made up of individual units which are not oscillators. In this study, we take advantage of a thermodynamic approach combined with the Ott-Antonsen theory. The thermodynamic framework produces an analytically tractable population models written in term of a partial differential equation (PDE), from which we extract the firing rate of the spiking network. The Ott-Antonsen theory allows further reduction and breaks down the PDE into a low dimensional system. Bifurcation analysis of the reduced system enables us to reveal how synaptic interactions and inhibitory feedback permit the emergence of macroscopic rhythms. The usual adjoint method can then be applied and a semi-analytical expression of the macroscopic infinitesimal PRC is derived. Our analytical computations allow us to make key predictions. First we observed that only stimulus targeting the inhibitory cells can generate a biphasic PRC. Such PRCs are known to facilitate entrainment to periodic inputs at both higher and lower frequencies than the natural frequency of the network. Then we investigate the effect of coupling strength on the dynamical emergence of phase locking mode within two bidirectionally coupled spiking networks. Within the framework of weakly coupled oscillators, we clarify why macroscopic

oscillations show phase relations that are persistent across time, and provide reasons for the reported diversity of phase lags between cortical regions. Our predictions are supported by extensive numerical simulations and are consistent with empirical data.

Disclosures: G.D. Dumont: None. **B. Gutkin:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

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Topic: I.06. Computation, Modeling, and Simulation

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the Volkswagen foundation

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Title: Using a non-linear interdependence approach to detect directional coupling from spike trains

Authors: *I. MALVESTIO[1,2,3], T. KREUZ[3], F. MORMANN[4], R. G. ANDRZEJAK[1]
[1]Univ. Pompeu Fabra, Barcelona, Spain; [2]Universitá degli Studi di Firenze, Florence, Italy; [3]Inst. For Complex Systems, Sesto Fiorentino, Italy; [4]Univ. of Bonn, Bonn, Germany

Abstract: The detection of interactions between different areas of the brain is a crucial problem in neuroscience. Connectivity detection is interesting not only at the population level (e.g. EEG, MEG) but also at the neuronal level, where connections between neurons are determined from their spike trains. For example, the study of connectivity using multi-unit recordings of spike trains from epilepsy patients can improve our understanding of how seizures spread from the focal area. Apart from the symmetric assessment of similarity between signals, an even more difficult task is the detection of the direction of the coupling. Depending on the characteristics of the data one can use different approaches. Here we describe a nonlinear interdependence technique [1] which applies the measure L [2] to point processes. This approach has the advantage of being modular, since it allows the use of different spike train distances [3] in order to gain complementary information about the data. With tests on Hindmarsh-Rose model system we show that this technique is robust to noise and able to deal with different dynamical regimes. In an application to intra-cranial recordings from epilepsy patients, we underline the importance of surrogate techniques which allow to assess the significance of our results. The Matlab source

codes of the measure L and of the spike train distances are available online [4].
[1] R.G. Andrzejak, T. Kreuz. EPL (Europhysics Letters) 96, 50012 (2011)
[2] D. Chicharro, R.G. Andrzejak. Physical Review E 80, 026217 (2009)
[3] T. Kreuz. Scholarpedia 6, 11934 (2011)
[4] http://ntsa.upf.edu/downloads; http://www.fi.isc.cnr.it/users/thomas.kreuz/sourcecode.html

Disclosures: I. Malvestio: None. **T. Kreuz:** None. **F. Mormann:** None. **R.G. Andrzejak:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

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Program#/Poster#: 092.06/UU56

Topic: I.06. Computation, Modeling, and Simulation

Support: Graduate Research Scholarship, University College London

Title: Computing with rates vs spikes: Fundamental differences in the dynamics of two different solutions to an integrator network

Authors: *J. A. MENENDEZ[1,2,3], P. E. LATHAM[1]
[1]Gatsby Computat. Neurosci. Unit, London, United Kingdom; [2]Sainsbury Wellcome Ctr. for Neural Circuits and Behaviour, London, United Kingdom; [3]Ctr. for Computation, Mathematics and Physics in the Life Sci. and Exptl. Biol., London, United Kingdom

Abstract: Neural networks are often modelled with units that communicate through continuous-valued firing rates. However, synaptic transmission arises via discrete action potentials, or spikes. Such spiking networks have been a long-standing interest of theoretical neuroscience, but their algorithmic properties are not as deeply understood as those of continuous rate networks. Here we investigate two classes of networks performing the same computation, one rate based and the other consisting of leaky integrate-and-fire (LIF) spiking neurons. The goal is to understand how the two networks solve the task, and whether they do so differently. Both networks integrate a sinusoidal input signal, and the value of the integral is given by a linear combination of the firing rates of the individual neurons. The readout weights are the same in both networks, allowing a direct neuron by neuron comparison. For the rate network, we follow Druckmann & Chklovskii (2012) to derive the recurrent weights needed to generate the desired rate dynamics; for the LIF network, we follow Boerlin et al (2013). We find that the resulting networks behave very similarly in the coding direction (the direction specified by the readout weights), but behave very differently in the non-coding directions. In particular, the dynamics of the spiking network are much higher dimensional than those of the rate network: whereas >90% of the variance in time-varying firing rates is concentrated along just one principal component in

the rate network, it is spread across 14 principal components in the LIF network. The first of these is aligned with the coding direction, but the others are not. We then ask whether these differences in the dynamics are due to different algorithmic solutions implemented by each network, or whether they instead reflect constraints imposed by the membrane potential dynamics present only in the LIF network. If the former is true, this example illustrates computational features idiosyncratic to spiking networks, and highlights that we should be careful in drawing conclusion about network circuitry from continuous rate-based network models. If the latter is true, then it suggests that some of the higher dimensional components of network dynamics in the brain may simply reflect the spiking nature of its neurons.

Disclosures: J.A. Menendez: None. **P.E. Latham:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

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Program#/Poster#: 092.07/UU57

Topic: I.06. Computation, Modeling, and Simulation

Support: NEI R01-EY024067

Simons Foundation Grant SCGB 325548

Title: A spiking model reveals mechanisms underlying dynamics of neuronal responses to optogenetic stimulation

Authors: *R. SHEWCRAFT[1], B. PESARAN[2]
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Abstract: Neuronal dynamics play a central role in the operation of neural circuits that generate flexible behaviors. The temporal structure in neuronal activity correlates with a variety of behavioral processes, such as decision making, perception, attention, and coordination. Optogenetics allows precise spatial and temporal control of neural activity patterns and may permit selective control of neuronal dynamics. In previous work, we measured neural activity during channelrhodopsin (ChR2) stimulation with trains of Poisson-distributed light pulses parametrically varying in pulse rate and pulse width. The dynamics of driven neural activity varied with pulse width, but not pulse rate. We found that the frequency range of the local field potential (LFP) that is driven by optogenetic stimulation was inversely proportional to the width of the stimulation pulses. A stimulation sequence with wider pulses drove LFP responses in a narrower frequency band.
In order to understand the mechanisms underlying the parametric control of neuronal dynamics,

we built a spiking neural network model incorporating ChR2 ion channels into integrate-and-fire neurons to simulate LFP responses to optogenetic stimulation. The model consisted of two components: (1) GABA, AMPA and leak channels derived from a model of LFP responses to visual stimulation (Mazzoni et. al., 2008) and (2) a model of ChR2 channels derived from photocurrents measured in vitro (Witt et. al. 2013). We computed the LFP as the sum of synaptic inputs onto excitatory cells in the model. The model faithfully captured the observed pulse width dependence of neuronal dynamics during optogenetic stimulation.
When compared to a simple linear model of responses to stimulation, the in vivo data showed less drive at high gamma frequencies (80-200Hz). This could be due to the ChR2 channels being unable to reliably track higher rates of stimulation. However, a reduction in the drive at high gamma was not present in our model. This suggests that the reduced high gamma drive may be due to recruitment of inhibition through network mechanisms, which were not built into the model, rather than a feature of the cellular mechanisms that belong to the model. These results demonstrate that spiking models can advance our understanding of the cellular basis of LFP responses to optogenetic stimulation. Additionally, we propose that spiking models may enhance the design of novel stimulation sequences to selectively control neuronal dynamics.

Disclosures: **R. Shewcraft:** None. **B. Pesaran:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.08/UU58

Topic: I.06. Computation, Modeling, and Simulation

Support: NSFC Grant 31371109

Title: Modeling distinct inhibitory cell circuits that orchestrate cortical theta, beta and gamma band oscillations

Authors: *X. ZHAO[1], G. CHEN[2], X. ZHANG[3], M. J. RASCH[1,4]
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Abstract: Distinct types of inhibitory interneurons are known to sculpt diverse rhythms of cortical oscillations, but how they interact to orchestrate specific band oscillations is mechanistically unclear. Our previous work used in vivo recording of optogenetic-tagged interneurons in primary visual cortex of awake mice to show that spiking of somatostatin (SOM)-and parvalbumin (PV)-expressing interneurons preferentially correlated with cortical beta (15-40 Hz) and gamma (40-80 Hz) band activities, respectively. Here, we present a

biophysically motivated computational mean-field model that mechanistically explains the experimental results based on the distinct interplay of the three neural populations, excitatory pyramidal cells, PV and SOM. We show that optogenetic perturbations of previous experiments can be well reproduced with the model and show further how cell populations distinctively control spontaneous theta, gamma, and visually-evoked beta oscillations in the model. Our computational modeling thus suggests that a circuit of the three cell populations suffices to generate realistic theta, beta and gamma oscillations as observed in experiments in mice. The model could serve as a stepping stone towards a "minimal standard model" for oscillatory patterns in local cortical circuits. We therefore developed additionally a simulation tool with graphical user interface for easy manipulation of connection strengths and the possibility of conducting virtual optogenetic experiments to enable hypothesis finding and intuition building that could guide future experimental investigations.

Disclosures: **X. Zhao:** None. **G. Chen:** None. **X. Zhang:** None. **M.J. Rasch:** None.

Poster

092. Spiking and Oscillation Models

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Program#/Poster#: 092.09/UU59

Topic: I.06. Computation, Modeling, and Simulation

Title: Self-generated up and down states in a spatially extended cortical network

Authors: *T. ARAKAKI[1], Y. AHMADIAN[2]
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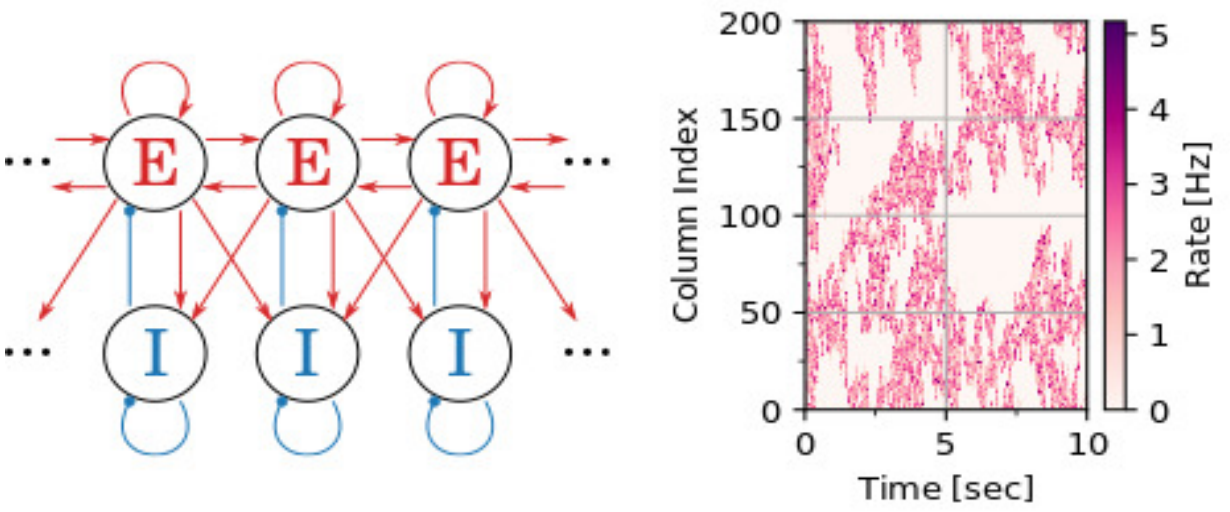
Abstract: During slow-wave sleep and types of anesthesia cortical networks transition between periods of sustained activity, called Up states, and essentially silent periods, called Down states. Studies in cortical slices and recent in vivo studies show that thalamic input is not necessary for sustaining Up states. This suggests that Up-Down states are self-generated by the cortical network, without external inputs.
Most theoretical treatments of Up-Down states are based on bistable rate models. Such models require either super-threshold external inputs or strong external noise to enable Down to Up transitions. However, strong external noise is inconsistent with the flat hyperpolarized membrane potentials observed during Down periods. To ameliorate this problem, these models rely on adaptation in excitatory cells which also drives the Up to Down transitions. We propose a simple alternative model based on non-adaptive excitatory and inhibitory spiking neurons, spatially organized in cortical columns, with synapses connecting neurons in the same or neighboring columns. Neurons receive no external inputs. We first show that a reduced two-column network is bistable, with Up state firing rates in the empirical range. In the multi-columnar case, active columns excite their silent neighbors, inducing them to transition to Up states. The Up state

activity thus rapidly spreads spatially, while self-generated spiking noise drives the Up to Down transitions. Consequently, our model's Down states are characterized by near flat membrane potentials consistent with empirical observations. Finally, as this mechanism does not rely on adaptation mechanisms with long time scales, it can unify the understanding of Up states, with that of transient bumps of membrane potential, as observed e.g. in auditory cortex, and hypothesized to be short variants of the Up state.



Disclosures: **T. Arakaki:** None. **Y. Ahmadian:** None.

Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIH NIBIB 1R01EB018297

NSF PoLS 1058034

Title: Heterogeneous inter- and intra-connectivity within E-I networks influences the effects of cholinergic modulation on synchronous oscillatory behavior of excitatory cells

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Abstract: Rhythmic dynamics in networks with interconnectivity between excitatory and inhibitory neural networks (E-I networks) have classically been explained by the Pyramidal Interneuron Network Gamma (PING) mechanism, which relies on strong reciprocal interconnectivity between the E and I networks and strong intraconnectivity among the I cells. This mechanism can be affected by the intrinsic properties of neurons, which is important considering many neurons found in E-I networks are modulated by acetylcholine (ACh). The presence of acetylcholine blocks the M-type potassium current and changes the neuron's Phase Response Curve (PRC) from Type II to Type I. The effect of ACh as well as changes to the connectivity strengths in E-I networks have profound effects on E cell dynamics, which may diverge from the predictions of classic PING theory.

In networks where both E and I cells respond to cholinergic modulation similarly, we investigated the role that the strength of inhibitory intraconnectivity plays in determining the dynamics of E-I networks. Indeed, Type I networks with weak inhibitory intraconnectivity can promote synchronous rhythmic E cell activity when excitatory-to-inhibitory (E-to-I) synapses are weak. Within synchronous E cell bursts, the cells fire in an organized and consistent fashion determined by their intrinsic firing frequencies. However as the E-to-I synaptic weight increases, the organization of cell firing within E cell bursts and the periodicity of these bursts breaks down. When inhibitory cell intraconnectivity is heterogeneous, consisting of two subnetworks, one strongly and one weakly connected, E cells exhibit organized and periodic activity over a wider range of E-to-I synaptic weights than networks with a strictly weakly or strongly connected inhibitory network. In contrast, similar networks containing Type II neurons do not exhibit dichotomous dynamics dependent upon the inhibitory cell intraconnectivity.

We further probe the intricacies of E-I network dynamics by examining the interaction between cell type and network connectivity. Our results show that when network interconnectivity is dominant over network intraconnectivity, E cell rhythms are driven by network connectivity via PING. However, when network intraconnectivity dominates network interconnectivity, E cell rhythms can be driven by PRC properties of Type II E cells and excitatory intraconnectivity instead of PING.

These results provide a better understanding of the multitude of dynamics that can arise from the canonical E-I network when various heterogeneities known to occur in the brain, both in network connectivity and cell type, are taken into account.

Disclosures: S. Rich: None. **V. Booth:** None. **M. Zochowski:** None.

Poster

092. Spiking and Oscillation Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: UK BBSRC grant BB/L000814/1

Title: An oscillatory neural network model with winner-take-all dynamics explains reaction times in visual search experiments

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Abstract: Winner-take-all (WTA) is a computational principle used in cognitive modeling to implement such functions as competitive learning, decision-making, action selection, attention, etc. According to this principle, the neurons in the system compete with each other for activation. Typically, only one neuron (neural population) with the highest activity elicited by the strongest input wins the competition, forcing other neurons to shut down their activity. Traditionally, in WTA systems, outputs compete for activation via lateral or recurrent inhibition. In this paper, we suggest a new approach to the WTA modeling that is based on synchronization in an oscillatory network with a central element. Consider a system of neural oscillators with the radial architecture of connections. This means that there is a central oscillator (CO) in the system that is connected with a set of the so-called peripheral oscillators (POs) by feedforward and feedback connections. We show that there is a possibility to organize a competition between POs for the synchronization with the CO in such a way that only one PO can win. Winning PO works coherently with the CO while other POs are out of phase with the CO. This leads to the resonant increase of the activity of the wining PO while the activity of the other POs will decrease to a low level.
We use this WTA oscillatory network to model the results of visual search experiments: POs correspond to different objects in the display and the CO plays the role of the central executive of the attention system. We assume that the strength of the connection from the "target" PO to the CO is higher than the strengths of connections to the CO from other POs, corresponding to distractors. This assumption increases the probability for the "target" PO to win the competition for the synchronization with the CO and, hence, for the target object to be included into the attention focus. The result of model simulations depends on the randomly selected initial values: in some cases these values are in the basin of attraction of WTA dynamics for the target but sometimes they are not. Based on the Guided Search Theory, massive model simulations provide estimations for the average number of selection attempts needed for the target object to be included in the attention focus. These estimates can be recalculated into reaction times. We show that the model correctly reproduces reaction times in visual search tasks of various complexities. Reaction times linearly depend on the number of objects in the display, which is in agreement with experimental evidence. This linearity was not a priori included in the model design; it appeared as a remarkable result of model dynamical properties.

Disclosures: R. Borisyuk: None. **Y. Kazanovich:** None. **O. Burylko:** None.

Poster

092. Spiking and Oscillation Models

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Program#/Poster#: 092.12/UU62

Topic: I.06. Computation, Modeling, and Simulation

Title: The tradeoff between oscillatory communication and neural computation

Authors: *E. PETERSON[1], B. VOYTEK[2]
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Abstract: Theoretical work on neural oscillations has focused on how oscillations improve neural coding, by organizing action potentials into synchronous windows of activity. Rarely is it addressed when and how oscillations might instead harm coding. Empirically, oscillatory disruption is reported in several neural pathologies, including Parkinson's disease, schizophrenia, and depression. These disruptions, however, present as both increases and decreases to oscillatory power, suggesting both too much and too little oscillatory modulation is harmful. We've derived a new theoretical tool (the 'voltage budget') to quantify the benefit, and the more importantly the cost, of oscillatory activity. In a series of simplified models we use this tool to define a set of inequalities that strictly separate optimal from pathological oscillatory activity.

Disclosures: E. Peterson: None. **B. Voytek:** None.

Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIBIB/NIH Grant 4P41EB001978-32

NIH grant U01 GM104604

DARPA grant N66001-14-C-4016

Title: Development of a computational model of mitochondria and its integration in a CA1 pyramidal neuron

Authors: J. SHANG[1], *J.-M. C. BOUTEILLER[2], G. J. YU[2], A. MERGENTHAL[2], E. Y. HU[2], T. W. BERGER[2]
[1]Northwestern Univ., Evanston, IL; [2]Biomed. Engin., USC, Los Angeles, CA

Abstract: The brain performs a wide variety of energy-dependent processes to accomplish its function. To shed some light on the interactions between neuronal function and its energy-dependent processes, we developed a computational model of mitochondria and placed instances of this model on a CA1 pyramidal cell in accordance with experimental findings. The distributed models respond to changes in local cytosolic calcium concentrations; they let calcium enter the inner mitochondria membrane, which consequently leads to an increase in their production of ATP. Additionally, given the dynamic nature of neuronal activity, efficient regulation of mitochondrial mobility is required to enable the rapid redistribution of mitochondria to different areas to meet changes in metabolic requirements. Our model therefore also accounts for mitochondria transport: we described the changes in position of the mitochondria in the neuron in accordance with reported observations, i.e. changes in local calcium dynamics and cytosolic ATP concentrations. We herein present details on the model implemented and some preliminary observations. Future work will consist in using this computational platform to test hypotheses put forth to explain dysfunctions leading to pathologies (e.g. calcium dyshomeostasis and mitochondria dysfunctions in AD and PD), but also as an in-silico testbed for the discovery of novel therapeutic avenues.

Disclosures: J. Shang: None. **J.C. Bouteiller:** None. **G.J. Yu:** None. **A. Mergenthal:** None. **E.Y. Hu:** None. **T.W. Berger:** None.

Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant U01 GM104604

NIBIB Grant P41 EB001978

ONR Grant N00014-13-1-0211

Title: Cellular and network contributions to place field formation and place encoding in the entorhinal-dentate system: A large-scale, computational, spiking neural network study

Authors: *G. J. YU, D. SONG, T. W. BERGER
USC, Los Angeles, CA

Abstract: Grid cells in layer II of the medial entorhinal cortex provide spatial information to the hippocampus that is used to generate internal representations of location, as evidenced by the formation of place cells within the CA3 and CA1 subfields and the expression of place fields by dentate granule cells. Many, theoretical, computational models have been proposed to explain the transformation of grid cell activity into place field formation which demonstrate that grid cell-like input and a competitive inhibition mechanism are minimum components necessary for the formation of place fields. However, these results were obtained using reduced and simplified neural networks and neuron models that characterize a general neural system but are not representative of any particular subfield of the hippocampus. To understand the biological conditions under which place fields emerge within the rat dentate gyrus, grid cell input was incorporated into our large-scale, biologically realistic, spiking neural network model of the rat entorhinal-dentate system which included 120,000 granule cells and 6,500 basket cells with the neurons modeled using a multi-compartment approach in NEURON. The network uses an anatomically derived topography to constrain the connectivity between the medial and lateral entorhinal cortices and the dentate neurons, and the network also includes feedback and feedforward inhibition mediated by the basket cells. To investigate place field formation, the spatial firing rate map constructed by the total presynaptic activity converging onto a granule cell was compared to the postsynaptic spatial firing rate map, i.e. the spatial firing rate map of the granule cell. The transformation of the postsynaptic rate maps as compared to their presynaptic rate maps was analyzed under different cellular (i.e. afterhyperpolarization) and circuit (i.e. feedforward and feedback inhibition strength) properties to characterize their contributions to place field formation. To assess the amount of spatial information that was encoded by the spatio-temporal patterns of the network at a fundamental level, a simple maximum likelihood decoder was implemented which uses the sum of the spatial firing rate maps of the granule cells that fired within a time window to decode position.

Disclosures: **G.J. Yu:** None. **D. Song:** None. **T.W. Berger:** None.

Poster

092. Spiking and Oscillation Models

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NIH Grant U01 GM104604

DARPA Grant N66001-14-C-4016

ONR Grant N00014-13-1-0211

Title: Modulation of CA1 region via muscarinic acetylcholine receptor activation - A computational study

Authors: *A. MERGENTHAL[1], J.-M. C. BOUTEILLER[2], T. W. BERGER[2]
[2]Biomed. Engin., [1]USC, Los Angeles, CA

Abstract: In the CA1 region of the hippocampus, several neuron types express receptors for acetylcholine (ACh). The distribution of these receptors among the primary excitatory neuron type suggests that incoming cholinergic signals could have widespread modulatory effects. These cholinergic signals can be disrupted either through the loss of cholinergic projections (as occurs in Alzheimer's disease) or through the alteration of ACh concentrations as occurs after exposure to certain exogenous compounds such as chemical weapons (e.g. sarin) as well as environmental toxins. This work uses a computational model of the CA1 cell network to explore how ACh concentration alters the cells' spiking dynamics. This model comprises three cell types (CA1 pyramidal cells, parvalbumin positive (PV+) basket cells, and cholecystokinin positive (CCK+) basket cells), all of which are known to express muscarinic acetylcholine receptors (mAChRs). These three cell types connect in a manner that allows feedforward inhibition, feedback inhibition, and/or disinhibition, depending on the relative activation of the cells. Modulation of cell activity is done using a kinetic model that links M1 mAChR activation to the inhibition of voltage gated potassium channels (Kv7). By exploring how Kv7 channel inhibition changes network behavior, we can better understand the modulatory role ACh plays on this network. In addition, understanding the normal functional ranges of network operations may facilitate the development of more efficacious therapies for pathological disturbances of ACh signaling.

Disclosures: A. Mergenthal: None. **J.C. Bouteiller:** None. **T.W. Berger:** None.

Poster

092. Spiking and Oscillation Models

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Program#/Poster#: 092.16/UU66

Topic: I.06. Computation, Modeling, and Simulation

Support: U01 GM104604

P41 EB001978

Title: Mechanistic and input-output models of calcium dynamics at the postsynaptic spine to enable cross-scale investigations of their effects

Authors: *E. Y. HU[1], J.-M. C. BOUTEILLER[1], A. MERGENTHAL[2], D. SONG[1], T. W. BERGER[1]
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Abstract: Calcium concentration in the postsynaptic spine is an important factor for many signal transduction pathways that lead to longer term processes such as synaptic plasticity. Calcium dynamics themselves are depend on multiple processes, such as influx through receptor channels and efflux through pumps, as well as spine properties such as volume and distance from the soma. Considering these factors leads to a computationally costly model that makes the study of these long-term processes at the network-level (i.e. with a large number of neurons and spines) impractical, if not impossible. Here, we present a computational model of calcium dynamics at the spine that takes two forms : (1) a mechanistic form, to understand how individual components, such as receptor channels and pumps, influence overall calcium activity and (2) an input-output model, which will extract the main dynamical features of the mechanistic model and enable large-scale simulations by reducing computational complexity resulting from the simulation of calcium. We demonstrate the validity of the models, and provide a simulated case study showing how calcium activity varies as a function of synaptic location along the dendritic tree. This work constitutes the foundation we will use to study spine calcium dynamics and its effects across multiple scales, to investigate the molecular mechanisms and potential pathogenic dysfunctions that affect calcium activity and their effects on network-level observables.

Disclosures: E.Y. Hu: None. **J.C. Bouteiller:** None. **A. Mergenthal:** None. **D. Song:** None. **T.W. Berger:** None.

Poster

092. Spiking and Oscillation Models

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Program#/Poster#: 092.17/UU67

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant 1045914

Title: A generalized phase response curve method for predicting the phase-locked mode of neural networks

Authors: *D. AUSTIN[1], S. OPRISAN[2]
[2]Physics & Astronomy, [1]Col. of Charleston, Charleston, SC

Abstract: Neurons are excitable cells that are silent most of the time and only briefly produce a burst of electrical activity called action potentials (APs) in response to inputs received from other neurons. The main mechanism used by neurons to respond and adapt to environmental stimuli is through changing their firing frequency proportional to inputs received. The relationship between the external stimulus timing and the change in the firing rate of the neuron is called a phase resetting curve (PRC). We successfully defined a recursive generalized PRC to account for multiple inputs per cycle a neuron may receive in more realistic networks. We tested our

generalized PRC on a biologically-relevant neural network motif with a driver-driven neuron such that the driven neuron also receives a feedback from an interneuron. We successfully derived analytical solutions for the phase-locked modes in a three-neuron network and they matched our numerical simulation results.

Disclosures: D. Austin: None. **S. Oprisan:** None.

Poster

092. Spiking and Oscillation Models

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Program#/Poster#: 092.18/UU68

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant 1045914

Title: Phase space reconstruction of optogenetic data using delay embedding

Authors: *S. OPRISAN[1], J. IMPERATORE[2], J. HELMS[2], T. TOMPA[3], A. LAVIN[4]
[1]Physics & Astronomy, [2]Col. of Charleston, Charleston, SC; [3]Med. Univ. of South Carolina, Charleston, SC; [4]Dept Neurosci, Med. Univ. South Carolina, Charleston, SC

Abstract: Gamma oscillations received significant attention lately due to their role in associative learning or memory recollection. The accepted paradigm is that gamma rhythm involves the reciprocal interaction between interneurons, mainly parvalbumin (PV+) fast spiking interneurons (FS PV+) and principal cells.
Male PV-Cre mice were infected with the viral vector delivered to the mPFC and allowed precise optical stimulation (473 nm laser light) of ChR2 expressing PV+ interneurons. Electrophysiological data were recorded using an optrode and the signal was band-pass filtered online between 0.1 and 130 Hz for local field potentials (LFP) recordings. We used a single, 10 ms duration, light pulse applied every 2 s and recorded with a sampling time of 0.1 ms. Each trial was repeated 100 times and we only retained and analyzed data from six animals that showed stable and repeatable response to optical stimulations.
We used nonlinear dynamics to reconstruct the phase space dynamics of mPFC from LFPs. For this purpose, we used the average mutual information to estimate the delay time and false nearest neighbor method to estimate the embedding dimension. The shape of the attractors for control and cocaine-injected groups were relatively stable and similar.

Disclosures: S. Oprisan: None. **J. Imperatore:** None. **J. Helms:** None. **T. Tompa:** None. **A. Lavin:** None.

Poster

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National Institute of Health through the Institutional Development Award (IDeA) Networks of Biomedical Research Excellence (INBRE) program.

Title: Scalar timing in memory: A temporal map in the hippocampus?

Authors: *T. J. AFT[1], S. A. OPRISAN[1], C. V. BUHUSI[2], M. BUHUSI[3]
[1]Physics, Col. of Charleston, Charleston, SC; [2]Interdisciplinary Program in Neurosci., [3]Dept. Psychology, Utah State Univ., Logan, UT

Abstract: Time perception in the second to minute range is essential for a wide variety of cognitive processes. Such tasks require accurate timing and involve many cortical areas such as prefrontal cortex, striatum, and hippocampus. Peak-interval procedures showed that dorsal hippocampus lesions could produce early responses, whereas ventral hippocampus lesions could produce delayed responses. From a theoretical perspective, it has been hypothesized that a ``memory constant'' must connect the reinforcement time with the time when the animal is maximally responsive (Gibbon et al. 1984; Gibbon Church 1984). It has been also shown that such a ``memory constant'' could be altered pharmacologically. We used a topological map of the hippocampus and produce both advances and delays in numerically simulate peak-interval procedures by mimicking spatially localized hippocampus lesions. Based on the topological map hypothesis, we derived a theoretical relationship between the ``memory constant'' and the location and the extent of hippocampus lesions.

Disclosures: **T.J. Aft:** 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 NSF CAREER IOS-1054914 grant to S.A.O. This project was also supported

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Poster

092. Spiking and Oscillation Models

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Topic: I.06. Computation, Modeling, and Simulation

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Title: Cross-area phase-amplitude coupling (CAPAC) as a measure of synaptic transmission

Authors: *B. NANDI[1], B. KOCSIS[2], M. DING[3]
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Abstract: Abstract
Cross-frequency coupling (CFC) evaluates the relationship between oscillatory activities in different frequency bands and has become a powerful tool for understanding the spatial and temporal organization of neural dynamics in both human and animal research. Among the various CFC measures, phase-amplitude coupling (PAC), which estimates the statistical dependence between the phase of a low frequency oscillation and the amplitude of a high frequency oscillation, is the most commonly used. To date, CFC PAC analysis has mainly been applied in a univariate fashion, namely, to characterize phase-amplitude coupling derived from the same signal. In this work, we consider the extension of PAC analysis to two signals, which may come from two different neuronal ensembles in the same or two different brain regions. Assuming that the high frequency oscillations (e.g., gamma) reflect population spiking, therefore the output activity of a neuronal ensemble, and that the low frequency oscillations (e.g., theta) reflect dendritic processing, therefore the input activity of a neuronal ensemble, we hypothesized that cross-area phase-amplitude coupling (CAPAC) may be used to infer the direction and strength of synaptic transmission. We tested our hypothesis on LFP data recorded from CA1 and dentate gyrus (DG) of the rat hippocampus and found that: (1) the amplitude of gamma oscillations in DG was significantly coupled to the phase of theta oscillations in CA1, but not vice versa, implying unidirectional synaptic transmission from DG to CA1 and (2) the magnitude of DG gamma and CA1 theta CAPAC was positively correlated with the magnitude of DG-->CA1 Granger Causality, a well-established analytical measure for inferring the direction and strength of synaptic transmission. These findings, in conjunction with the anatomical ground truth predicting DG-->CA3-->CA1 (tri-synaptic pathway), lend support to our hypothesis.

Disclosures: B. Nandi: None. **B. Kocsis:** None. **M. Ding:** None.

Poster

092. Spiking and Oscillation Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIMH Intramural Program

Title: Emergence of nonlinear

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Abstract: The ability of the brain to perform complex tasks is generated by interacting networks implementing simpler computations, e.g. linear filtering and normalization. Even though this ability is partially emulated by computational models of networks with spiking neurons, our understanding of the mechanisms generating computations in neural networks is limited. Current theories are based on the balanced-state model which can explain the irregular firing observed in cortex and also accounts for other experimental data, such as wide firing rate distributions and weak correlations. A key prediction of the model is that the network should have a linear transfer function; this prediction is problematic because it severely constrains the computation that can be implemented.
Nonlinearities can be generated by short-term plasticity but the degree to which synapses are facilitated or depressed in vivo is not known.
An outstanding open question is therefore if, and how, nonlinear computations can be implemented by neural networks with linear synapses while maintaining irregular firing.
The transfer function of recurrent networks of excitatory and inhibitory neurons has been derived for networks of binary units and current-based spiking neurons with strong synaptic coupling. We investigated networks of spiking neurons of increasing biological accuracy, including the effects of: moderate coupling, synaptic conductance and synaptic current dynamics. We showed numerically and analytically that the coupling strength plays a fundamental role in shaping the network response. We found that in spiking conductance-based networks, as in current-based networks, the response is linear in the limit of strong coupling. Nonlinearities appear for moderate coupling while preserving a highly irregular firing. The type of nonlinearity (e.g. supra-linear vs sub-linear) is determined by the structure of the connectivity matrix.
Interestingly, to obtain the strong coupling limit in conductance-based models, a specific scaling relation between the synaptic strength and the number of connection per neuron is required. This scaling relation is distinct from the current-based case, and is compatible with recent experimental data in culture preparations.

Our work provides a microscopic foundation to rate models proposed to explain normalization and surround suppression in visual cortex. It could be used as a tool to infer parameters of the connectivity matrix of cortical circuits from optogenetic stimulation experiments, and to improve our understanding of the computations performed by these circuits.

Disclosures: A. Sanzeni: None. **M.H. Histed:** None. **N. Brunel:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.22/UU72

Topic: I.06. Computation, Modeling, and Simulation

Title: Making accessible the transistor channel approach for studying conductance-based models: The dynamics of a silicon neuron analog of the Hodgkin-Huxley equations

Authors: J. O. HASLER[1], *S. M. BAER[2]
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Abstract: Neuromorphic engineering started with the explicit goal of building a bridge between neuroscience and engineered systems (Mead 1990). Only a few systems have contributed knowledge back to neurobiology (Lazzaro et al. 1988, George et al. 2013, Koziol 2014). In this study, a new computational neuroscience framework is utilized to interpret physically implemented neural models on SoC FPAA devices. Specifically, the objective is to apply the transistor channel approach to construct a silicon neuron circuit (Si circuit) analog of the Hodgkin-Huxley (HH) model and analyze the dynamics of the model using singular perturbation and bifurcation methods. In addition, experimental data generated from the physical circuit is compared and contrasted to the numerical results (digital) generated from the Si neuron mathematical model and the corresponding established Hodgkin-Huxley model. Checked for consistency is the bifurcation structure in the Si mathematical model to the Si circuit data. We find that Si circuit values of the current I at the Hopf bifurcation points compare well to the values predicted from a linear stability analysis of the mathematical models. Also, we find that for both the Si mathematical model and the established HH model the directions of bifurcation (supercritical or subcritical) are consistent, as well as dynamic bifurcation onsets (slow ramping of current). The results of this study serve as a starting point for more systematic investigations of Si neurons and networks based on realistic morphologies. For example, using the transistor channel approach to build dendritic cable analog circuits that incorporate not only channel properties, but the details of dendritic morphology, including dendritic tapering, varicosites, excitable and activity dependent dendritic spines of different shapes, configurations, and spatial distributions.

Disclosures: **J.O. Hasler:** None. **S.M. Baer:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.23/UU73

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH/NINDS Grant P50-NS098685

NIH Grant OD P51-OD011132

Title: An empirical analysis of phase amplitude coupling

Authors: *M. CAIOLA[1,3], T. WICHMANN[1,2,3]
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Abstract: By using electrophysiological techniques, one is able to record a wealth of neural oscillations such as local field potentials (LFPs) and electroencephalography (EEG) recordings. To properly analyze these oscillations there are a several forms of cross frequency coupling procedures available. One such method, phase amplitude coupling (PAC), is a measure of how correlated a signal's amplitude changes are to that of specific phase bands. This is commonly done by calculating the "modulation index" (MI), using the entropy based Kullback-Leibler distance method, with a higher MI representing a larger amount of coupling. PAC has been suggested to play a role in sensory integration, memory process, and attentional selection. More recently, PAC abnormalities have been identified as a pathophysiologic feature of Parkinson's disease. The EEG of parkinsonian patients has been shown to have a large MI between beta phase and gamma amplitude, that was not seen for dystonic and epileptic patients. Further studies in parkinsonian patients showed that therapeutic deep brain stimulation can diminish the PAC, while our studies in parkinsonian nonhuman primates have showed similar effects with STN stimulation and levodopa treatment. Unfortunately, this approach can be prone to low phase noise and false positive detection of abnormal PAC values.
In the current study, we surveyed the impact of various filter designs on the PAC detection results. We also examined how the duration of sampled data affects PAC detection, and whether artifacts in the signals are a major concern. For all analysis, we used simulated LFP data, thus having full control over the frequency content of the source signals. Finally, we explored possible future refinements for PAC by implementing wavelet approaches, nonsinusoidal analysis, and 3D representations of PAC through time. We found that the precision and sensitivity of PAC detection is strongly dependent on all of these factors. Further optimization of the current algorithms to render it less sensitive to filter parameters, duration of the sampled

signals, or artifacts, may be necessary to increase the usefulness of this tool, especially if one intends the analysis to be comparable to other studies.

Disclosures: M. Caiola: None. **T. Wichmann:** None.

Poster

092. Spiking and Oscillation Models

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 092.24/UU74

Topic: I.06. Computation, Modeling, and Simulation

Support: Marie Sklodowska-Curie Action Individual Fellowship (H2020-MSCA-IF-2015) under grant agreement number 699829 ("ETIC")

Marie Sklodowska-Curie Action Individual Fellowship (H2020-MSCA-IF-2014) under grant agreement number 659227 ("STOMMAC")

Deutsche Forschungsgemeinschaft (Collaborative Research Center 889, C1)

Title: Information jitter derivative method: A novel approach to the analysis of multiplexed neural codes

Authors: *M. MOLANO-MAZON[1], A. ONKEN[1], J. K. LIU[2,3,4], T. GOLLISCH[2,3], H. SAFAAI[1,5], S. PANZERI[1]
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Abstract: How to mathematically separate out the different components of a neural code and to identify the unique contribution of each of these components to sensory coding and behavior is an open question in neuroscience. Here we present a novel approach to decompose the information encoded in the temporal structure of a spike train into the unique, complementary information contained in its different temporal scale components. We do this by analytically inferring the derivative of the information with respect to the precision with which the neural activity is measured. We demonstrate that the negative of this derivative represents the non-redundant information carried by each temporal scale and therefore constitutes an exact breakdown of the total information. The proposed approach, which we called Information Jitter Derivative (IJD) method, uses a jitter procedure to manipulate the precision of the neural activity and allows to precisely identifying the relevant timescales in the encoding of the stimulus information. We validated the IJD method on simulated and real data. In particular, we show that the IJD is able to uncover the different strategies used by the retinal ganglion cells of the axolotl

salamander to encode information about different visual features. Importantly, we found that coarse and fine spatial features are encoded into different temporal scales. The Information Jitter Derivative method thus provides a way of studying in detail the information processing capabilities of a multiplexed neural code by breaking down the temporal information contained in the neural activity into its unique, complementary temporal scale components.

Disclosures: M. Molano-Mazon: None. **A. Onken:** None. **J.K. Liu:** None. **T. Gollisch:** None. **H. Safaai:** None. **S. Panzeri:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.01/UU75

Topic: I.06. Computation, Modeling, and Simulation

Support: CRITICAL PATH

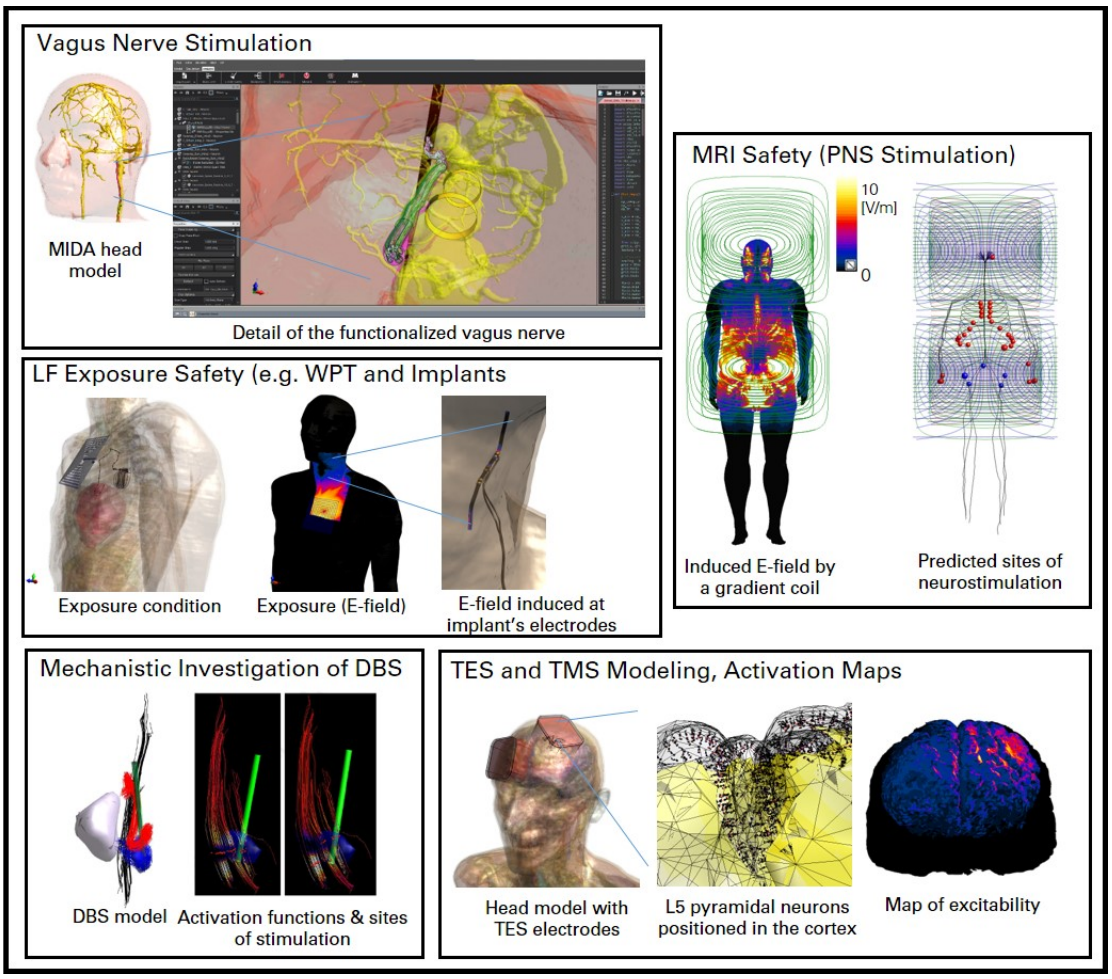
Swiss Commission for Technology and Innovation CTI (S4L-CAPITALIS: 14930.1 PFLS-LS)

Title: Functionalization of anatomical human models with electrophysiological neuronal models for neurostimulation related mechanisms and safety investigations, device development, personalized treatment planning, and in silico trials

Authors: *A. M. CASSARA[1], E. NEUFELD[1], H. MONTANARO[1,2], N. KUSTER[1,2]
[1]IT'IS Fndn., Zurich, Switzerland; [2]Swiss Federal Inst. of Technol. (ETHZ), Zurich, Switzerland

Abstract: The emerging electroceuticals and neuroprosthetic devices, which primarily target the peripheral nervous system (PNS), and the various neuromodulation therapies acting on the central nervous system (CNS; i.e., brain and spinal cord) require assessment of efficacy (e.g., neuron type & spatial selectivity, stimulation vs. conduction blocking, synchronization & latency, etc.) and safety (e.g., undesired side-effects). This is difficult due the complexity of *in vivo* exposure conditions (related to anatomical and tissue property variability) and their interplay with the non-linear neuronal electrophysiology and the sophisticated neuromorphology. Therefore different neuro-functionalized computational anatomical models were developed that feature coupled EM-electrophysiology simulations with realistic neuronal models (e.g., pyramidal neurons physiologically placed in the corresponding cortex layers, STN and GPi neurons⋯) and axons following PNS trajectories (partly embedded in multi-fascicular nerve models). These models were successfully applied to i) investigate neurostimulation mechanisms; ii) ideate novel therapeutic approaches (e.g., non-invasive temporal interference deep brain stimulation) iii) develop and optimize devices; iv) personalize treatments (e.g., multi-contact-

electrode steering parameters and pulse shapes for selective stimulation); v) perform *in silico* clinical trials partially replacing animal and human trials; vi) assess safety issues related to low frequency (LF) exposure (wireless power transfer (WPT), MRI scanners, ⋯) in the presence and absence of implants, identifying problematic assumptions behind current safety standards. Predictions have been validated against own and 3rd party experimental data (thresholds, recruitment curves, selectivity⋯). Extensively neuro-functionalized high resolution anatomical models are thus a valuable tool for the neuromodulation community.



Disclosures: **A.M. Cassara:** None. **E. Neufeld:** None. **H. Montanaro:** None. **N. Kuster:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.02/UU76

Topic: I.06. Computation, Modeling, and Simulation

Title: Human activity recognition based on features extraction analysis

Authors: *I. EL MOUDDEN[1], M. OUZIR[3], A. BAJJOU[4], S. AMZAZI[3], S. EL BERNOUSSI[2]
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Abstract: Pattern recognition is an interesting research area, especially for human activity recognition. The purpose of human activity recognition study is to automatically detect human activities from the information acquired from different sensors using statistical techniques. Generally applied in healthcare and security management, human activity recognition stills a challenging task because of high dimensionality problems. Several approaches have recently been developed to solve these problems. In this paper, linear and nonlinear dimensionality reduction approaches based on Sliced Inverse Regression (SIR) and Kernel Principal Components Analysis (Kernel PCA) has been performed on a human activity recognition publicly available dataset built from the recordings of 30 subjects performing six different activities (Walking, walking upstairs, walking downstairs, sitting, standing, laying) and wearing a smartphone with embedded inertial sensors. The analysis of features extracted data has been done using two different classifier algorithms; Decision Tree (C5.0) and K-Nearest Neighbors (KNN). After dimension reduction, the number of factors was effectively reduced from p=561 to k=8. The results of class prediction show that the best accuracy is obtained by Kernel PCA-KNN followed by Kernel PCA-C5.0, SIR-C5.0, and SIR-KNN for k=26. In addition, for k=15 and k=8 the best accuracy is obtained by Kernel PCA-KNN followed by Kernel PCA-C5.0, SIR-KNN and SIR-C5.0. Taken together, the feature extraction and pattern recognition approaches described in our work deal perfectly with high dimensionality in human activity recognition dataset by minimizing the number of features and maximizing the classification accuracy.

Disclosures: I. El Moudden: None. **M. Ouzir:** None. **A. Bajjou:** None. **S. Amzazi:** None. **S. El Bernoussi:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant RO1 GM098578

NIH Grant RO1 GM111293

Title: A network mechanism for hysteresis in human brain networks during loss and recovery of consciousness

Authors: *H. KIM, J.-Y. MOON, G. A. MASHOUR, U. LEE
Univ. of Michigan, Ann Arbor, MI

Abstract: How the human brain loses and recovers consciousness after a major perturbation is an important question with significant neuroscientific and clinical implications. Hysteresis phenomena, i.e., a discrepancy in forward and reverse pathways reflecting a tendency to maintain a previous state, is observed during the entry into and exit from the state of general anesthesia. Since hysteresis is a universal phenomenon observed in physics, biology, and engineering, we hypothesized that the well-established mechanism of hysteresis in physics may be applicable to state transitions in the human brain.
To test this hypothesis, we performed a computational model study and empirical data analysis. The state of consciousness in healthy subjects was modulated with a general anesthetic during the recording of high density electroencephalogram (EEG). We also developed a brain network model that includes a feedback process in the regional interactions and that reflects the efficacy of an anesthetic. Using the model, we investigated the effects of various feedback processes and network structures (human, random, and scale-free) on hysteresis, searching for effective parameters that modulate the state transition. The model predictions were then tested with empirical data.
First, the model study suggests that hysteresis is a generic feature when a network with a feedback process undergoes a state transition, regardless of the type of feedback process and network structure. Second, stronger feedback processes result in a larger hysteresis. Third, the model explains empirically observed state transitions during anesthesia: (1) higher potency of anesthetic, larger hysteresis; (2) larger frequency difference of EEG, easier transition to unconsciousness; and (3) dissociable reconfigurations of the network structure and strength during loss and recovery of consciousness.
The model study and empirical data analysis suggest that the hysteresis in behavioral responsiveness during anesthesia is a generic network feature of state transitions. These findings support the hypothesis that state transitions between human consciousness and unconsciousness are grounded in the same principles as state transitions of complex networks, especially during perturbation.

Disclosures: H. Kim: None. **J. Moon:** None. **G.A. Mashour:** None. **U. Lee:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.04/UU78

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF EPSCoR Award Number 1632738

Title: A Gaussian process model of human ECoG data

Authors: *L. L. OWEN, J. R. MANNING
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Abstract: Human Super EEG entails measuring ongoing activity from every cell in a living human brain at millisecond-scale temporal resolutions. Although direct cell-by-cell Super EEG recordings are impossible using existing methods, here we present a technique for inferring neural activity at arbitrarily high spatial resolutions using human intracranial electrophysiological recordings. Our approach relies on two assumptions. First, we assume that some of the correlational structure of people's brain activity is similar across individuals. Second, we resolve ambiguities in the data by assuming that neural activity from nearby sources will tend to be similar, all else being equal. One can then ask, for an arbitrary individual's brain: given what we know about the correlational structure of other people's brains, and given the recordings we made from electrodes implanted in this person's brain, what would those recordings have looked like at other locations throughout their brain? We applied our approach to a large ECoG dataset comprising recordings from 67 epilepsy patients as they studied and recalled random word lists. We tested our approach using a cross-validation procedure whereby we predicted the recordings from a held-out electrode and compared the SuperEEG-derived estimate to the observed recording.

Disclosures: L.L. Owen: None. **J.R. Manning:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.05/UU79

Topic: I.06. Computation, Modeling, and Simulation

Support: Keefer Junior Faculty Funds (Beloit College)

Title: Validation of a murine seizure detection algorithm on human intracranial EEG

Authors: *R. A. BERGSTROM, J. CHEONG, B. A. DAHLBERG, E. W. BAXTER, C. J. FISHER, N. FORREY, N. D. FROIKIN, J. GARCIA, J. HUNHOFF, J. SANTOS-AREVALO, D. STOCKTON, X. XIE, Y. XUE
Biol., Beloit Col., Beloit, WI

Abstract: Though the cellular basis of seizure in murine models of epilepsy is fundamentally the same as that of seizures associated with epilepsy in humans, analysis of electroencepahlogram (EEG) signals in the two species require different, but equally time-consuming, considerations for visual signal analysis. A seizure-detection algorithm originally validated on murine intracranial EEG may not, therefore, be easily applied to human EEG. Here we analyze and optimize the performance of a published murine wavelet- and line-length-based EEG analysis algorithm (Bergstrom et al. 2013) on human data. Human multi-channel intracranial EEG data was obtained from ieeg.org, and one-hour sections of data were visually analyzed to establish seizure onset and locus. Relatively normal stretches of EEG (up to 5 minutes that do not contain epileptiform discharges or seizure-like activity in any channel recorded) were selected by eye as baseline signal for channel-specific thresholding by the algorithm. Algorithm output was compared to visual scoring to determine algorithm performance. Using published algorithm parameters optimized for murine seizure detection does not reliably quantify seizure activity in human EEG, even though the EEG signals of humans and mice may share similar characteristics under seizure conditions. However, the algorithm threshold and performance is tunable through modifications to the thresholding parameters and event definitions. With these slight modifications, the algorithm was able to correctly identify and quantify seizure content in human patient records with high reliability. This type of automated seizure identification is useful for long-term patient monitoring in the clinical setting and for diagnosis and identification of seizure locus in preparation for resection surgery. That the algorithm is flexible for use in multiple patient and species settings suggests that the combination of line length and wavelet analysis is a robust method for seizure identification and quantification in basic and translational research and clinical settings.

Disclosures: R.A. Bergstrom: None. **J. Cheong:** None. **B.A. Dahlberg:** None. **E.W. Baxter:** None. **C.J. Fisher:** None. **N. Forrey:** None. **N.D. Froikin:** None. **J. Garcia:** None. **J. Hunhoff:** None. **J. Santos-Arevalo:** None. **D. Stockton:** None. **X. Xie:** None. **Y. Xue:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.06/UU80

Topic: I.06. Computation, Modeling, and Simulation

Title: A computational model of epidural electrical stimulation of the cervical spinal cord in non-human primates

Authors: *N. GREINER[1,2], B. BARRA[2], S. BORGOGNON[2], G. SCHIAVONE[1], S. LACOUR[1], J. BLOCH[3], E. M. ROUILLER[2], G. COURTINE[1], M. CAPOGROSSO[2]
[1]Ctr. for Neuroprosthetics, Brain Mind Inst., EPFL, Geneve, Switzerland; [2]Domain of

Neurophysiology, Dept. of Med., Univ. of Fribourg, Fribourg, Switzerland; [3]Ctr. Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Abstract: Cervical spinal cord injury alters the communication between the brain and the spinal circuits controlling movement, often leading to tetraplegia. Epidural Electrical Stimulation (EES) of the lumbar spinal cord has shown promising results to restore leg motor control after paralysis. EES modulates the activity of proprioceptive afferent circuits, enabling the spinal cord to elaborate coordinated movements of previously paralyzed limbs. Similar proprioceptive afferent circuits contribute to upper-limb motor control, suggesting that EES may also improve the recovery of upper-limb movements after injury. The ability to engage individual or small groups of muscles is essential to facilitate motor control with EES. At this stage, however, this ability remains largely unexplored.

To address this question, we developed a realistic Finite Element/axon-cable biophysical model of EES applied to the non-human primate cervical spinal cord. Our objective was to evaluate and optimize the specificity of tailored, dura mater-like electrode implants placed dorsally over the spinal cord. The anatomically realistic model was derived from CT-scan acquisitions that supported 3D-reconstruction of the cervical vertebrae. We inserted physical compartments for the electrode silicone paddle and for the spinal roots, and used curvilinear coordinates to represent the white matter and spinal roots conductivity anisotropy.

We used the model to quantify the recruitment of Group I and Group II afferent fibers in the dorsal roots, motor axons in the ventral roots, and large myelinated fibers in the dorsal columns. To validate our model, we estimated the muscle responses to single pulses of EES using a realistic connectivity model between Ia-afferents and motoneurons innervating upper-limb muscles. We then compared our results to experimental recordings performed in two macaque monkeys under anesthesia.

We found a high correlation between the responses derived from simulations and obtained in vivo. However, the anatomical features exerted a non-negligible impact on the predicted recruitments. These results emphasize the importance of including realistic anatomical features to derive implant specificity from computer simulations.

Finally, we found that lateralized epidural stimulation of the cervical spinal cord recruits individual dorsal roots at significantly lower thresholds than other neighboring structures, suggesting that targeted EES could selectively modulate upper-limb motor pools. Taken together, these results establish the framework for the design of targeted cervical implants to facilitate upper-limb movements after spinal cord injury.

Disclosures: **N. Greiner:** None. **B. Barra:** None. **S. Borgognon:** None. **G. Schiavone:** None. **S. Lacour:** None. **J. Bloch:** None. **E.M. Rouiller:** None. **G. Courtine:** None. **M. Capogrosso:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.07/UU81

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF CCF-1350314

CMU BrainHub

CMU College of Engineering DOWD Fellowship

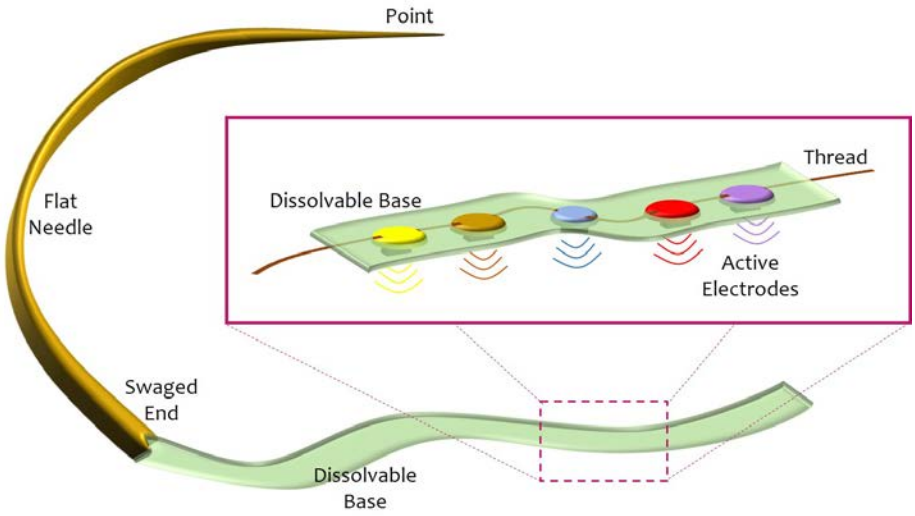
Title: Ultra-resolution subdermal eeg: Long-term minimally-invasive brain monitoring

Authors: *P. VENKATESH, A. KRISHNAN, J. WELDON, S. KELLY, P. GROVER
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Scalp EEG has long been the modality of choice to non-invasively diagnose epilepsy and traumatic brain injury (TBI). While traditional scalp EEGs are low resolution, recent work has shown through theory and experiments that high-density scalp EEG can provide higher resolution than traditional low-density systems. Accurate imaging, however, is predicated on good electrode-skin contact, low impedance and precise knowledge of the positions of electrodes: conditions that are difficult to meet for long-term recordings with current scalp EEG caps in ambulatory settings.

In order to enable in-home, continuous monitoring of patients with epilepsy/TBI, we propose Ultra-Resolution (UR) Subdermal EEG as a novel minimally invasive solution. Closely-spaced active electrodes are placed on a narrow biocompatible dissolvable base that is sewn into the scalp. The electrodes are attached to active circuits for amplification and wireless transmission of data. A thread connecting the electrodes allows us to retrieve the device after the measurement period is complete. Most importantly, because these subdermal electrodes are not in contact with the brain, they can reduce the possibility of brain infection in comparison with current Electrocorticography (ECoG) systems. Our subdermal electrode design is therefore a sterile, portable, minimally invasive solution for high resolution, long-term EEG measurements.

We postulate that UR Subdermal EEG has the added benefit of having higher imaging resolution than high-density scalp EEG. We validate this claim by deriving theoretical limits on the resolution of subdermal EEG, and comparing these with the corresponding limits for scalp EEG. We also provide simulations that contrast the performance of UR subdermal EEG with that of high-density scalp EEG, suggesting that our holistic approach to the design of high-density subdermal systems can lead to improved diagnoses and treatments for epilepsy and TBI.



Disclosures: **P. Venkatesh:** None. **A. Krishnan:** None. **J. Weldon:** None. **S. Kelly:** None. **P. Grover:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.08/UU82

Topic: I.06. Computation, Modeling, and Simulation

Support: Cooperative Agreement Number W911NF-10-2-0022

Title: Decomposing phase synchronization measures of scalp EEG

Authors: ***C. I. O'MALLEY**[1,2], M. VINDIOLA[2], J. M. VETTEL[2,3,4], S. M. GORDON[1,2]
[1]DCS Corp., Alexandria, VA; [2]US Army Res. Lab., Aberdeen Proving Ground, MD; [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Functional connectivity methods capture interactions among brain regions that rapidly form and dissolve coherent networks in support of task performance. For EEG data, phase-based methods assess functional connectivity by measuring the extent to which two disparate brain regions exhibit consistent phase differences. Current approaches calculate phase relationships either from scalp EEG or after blind source separation. In the former, connectivity estimates can suffer from volume conduction and muscle artifacts, while the latter case assumes the EEG data is composed of mutually independent sources that can be easily separated. Here, we propose solving the decomposition after the computation of the phase synchronization. Thus, the data is decomposed in a higher dimensional space where a limited number of phase locked source pairs

represent most of the signal variance.
To create known network activity, we use a neural mass model (NMM) to generate time series from two pairs of individually connected sources. Each pair of sources, or simulated brain regions, were connected at different, but overlapping times. These signals were mixed with between 0 and 4 channels of unconnected noise sources and projected to four simulated scalp electrodes.
In our analysis, we compared the effect of computing connectivity first and decomposition second (CD) to the opposite order (DC). Weighted phase lag index (WPLI) was used to calculate functional connectivity. Both independent component analysis (ICA) and principal component analysis (PCA) were tested for the decomposition step. In total there were four different analyses: CD-ICA, DC-ICA, CD-PCA, and CD-PCA/ICA. Statistical significance of the estimated connectivity from the four analyses was determined by creating a null model of the data which had been phase shuffled to remove synchronized activity. The original simulation and null model connectivity estimates were compared using a Wilcoxon rank sum test, then significance was determined using Bonferroni corrected p value. Results were averaged over 50 trials with randomized mixing matrices.
We analyzed how well each of the four analyses recovered the true number of connected sources (or regions) as well as the correct onset of each connection. Two sources were considered connected only if they remained significantly connected for more than .5s. Our results show that ICA is better at accurately determining the onset of the connections when computed before computing WPLI. PCA is better at determining the number of connections when computed from the pairwise WPLI estimates. These results indicate promising approaches to improve the connectivity estimates from EEG data.

Disclosures: C.I. O'Malley: None. **M. Vindiola:** None. **J.M. Vettel:** None. **S.M. Gordon:** None.

Poster

093. Functional Monitoring and Stimulation

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Program#/Poster#: 093.09/UU83

Topic: I.06. Computation, Modeling, and Simulation

Support: the GIST Research Institute (GRI) grant funded by the GIST in 2017

the National Research Foundation of Korea (NRF-2016R1A2B4010897)

Title: Multi-scale model for HD-tDCS and conventional tDCS - Targeting primary motor cortex

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Abstract: 1. Introduction. Conventional transcranial direct current stimulation (C-tDCS) is a non-invasive approach that delivers a weak direct current (~2mA) to evoke neural excitability, using two large rectangular electrodes. As C-tDCS affects a relatively wide area of the cortex, resulting in poor spatial targeting, new electrode arrangements called high-definition tDCS (HD-tDCS) was introduced to improve spatial focality. HD-tDCS uses small disc-type electrodes such that anode is placed on the target area and surrounded by four return electrodes. The focalized electric field directly beneath the anode induced by HD-tDCS was recently revealed via computational study; however, the cellular targets for HD-tDCS and C-tDCS remain unclear. Thus, we aim to study the neural excitability induced by HD-tDCS and C-tDCS using multi-scale models that combine a volume conductor model of the head (head model) and compartmental models of cortical neurons.
2. Methods. For the multi-scale model, we first constructed two types of the head model for C-tDCS and HD-tDCS using magnetic resonance imaging, respectively. For C-tDCS, two large rectangular electrodes (5x5 cm^2) were modeled with anode to target M1 (primary motor cortex) and cathode at the contralateral supraorbital area. For HD-tDCS, disc-type electrodes were attached to the scalp according to 4 by 1 electrode montage. Next, existing models of multi-compartmental models of layer 5 pyramidal neurons (L5 PNs) were taken from cat visual cortex, and we modified the dimension of PNs to fit the irregular geometry of the cortex; it was implemented in the NEURON. Then, electric potentials were calculated at each center point of each compartment of PNs and applied by extracellular stimulation.
3. Results and Discussion. We analyzed the steady-state membrane polarizations of L5 PNs. Both C-tDCS and HD-tDCS showed comparable spatial distributions of polarizations, resulting in hyperpolarization in the apical dendrites, axon crossing boundary between gray matter and white matter, and bending part, and depolarization in the basilar dendrites, soma, and axon terminal. In addition, we found about 2 times higher somatic polarizations in HD-tDCS (0.02 mV) compared to C-tDCS (0.013 mV). In conclusion, higher polarizations in HD-tDCS compared to the case for C-tDCS was observed. It may be due to the wider distributions of C-tDCS induced electric field, focused on brain areas between electrodes, while HD-tDCS showed relatively focalized electrical field directly underneath the anode.

Disclosures: H. Seo: None. **S.C. Jun:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

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Topic: I.06. Computation, Modeling, and Simulation

Support: UK BBSRC BB/L018268/1

UK EPSRC EP/N002474/1

Title: Prometheus: Computational optogenetics using cloud computing

Authors: *K. NIKOLIC[1], B. D. EVANS[2]
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Abstract: Optogenetics has flourished as a key technology for the deconstruction and control of brain circuits, with new applications rapidly emerging across the domain of neuroscience and beyond. The first clinical trials on humans have started recently, yielding very encouraging initial results. To extend the technology's biomedical applications, new opsin variants are continually being synthesized providing a wide range of characteristics to choose from (e.g. ion selectivity, spectral sensitivity, kinetics). In order to characterize, understand and apply various (rhod)opsins, we have developed an integrated suite of open-source, multi-scale computational tools called PyRhO [1,2]. The seamless integration of model fitting algorithms with simulation environments for these virtual opsins will enable neuroscientists to gain a comprehensive understanding of their behaviour from a limited set of experimental data and then run virtual experiments *in silico*. In this way, we expect PyRhO will help to significantly improve optogenetics as a tool for transforming biological sciences. The module is written in Python and the developed tools are now available as a Python package and as a Virtual Machine. While standard for computational scientists, these methods of obtaining software might still prove inconvenient for some, particularly experimental scientists. Consequently we now offer PyRhO as a cloud computing platform (dubbed *Prometheus*) with all dependencies and relevant modules already in place, allowing the user to immediately start benefiting from PyRhO's capabilities. Accessible via a Jupyter notebook GUI, it allows models to be fit, simulations to be run and results to be shared through simply interacting with a webpage: http://try.projectpyrho.org. Furthermore, this portal is more broadly useful for running virtual experiments in neuroscience and exploring the physiology of excitable cells in general due to its inclusion of the two most popular platforms for simulating detailed neuron models (NEURON) and neural networks (Brian). Our GUI offers simple and intuitive specification of the ion-channels and cell parameters as well as stimulation protocols together with seamless output visualization. Prometheus is a valuable tool for both educational and research purposes and offers easy reproducibility of simulation results, an important issue for science in general. This portal will have abundant capacity for expansion (e.g. building a database of opsin models, cell types, neural networks).
[1] Evans BD, Jarvis S, Schultz SR and Nikolic K, *Front. Neuroinform.* 10:8 (2016). [2] Evans BD and Nikolic K, *IEEE BioCAS Conf*, pp. 316-319 (2016).

Disclosures: K. Nikolic: None. **B.D. Evans:** None.

Poster

093. Functional Monitoring and Stimulation

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Human Frontier Science Program (HFSP)

Columbia Data Science Institute ROADS program grant

Title: Spatiotemporal modeling of resting state neuronal activity in the awake mouse brain

Authors: *S. H. KIM[1], M. A. SHAIK[2], Y. MA[2], H. T. ZHAO[2], D. N. THIBODEAUX[2], M. KHABBAZIAN[3], T. ZHENG[3], E. M. HILLMAN[2]
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Abstract: Since the advent of resting state functional connectivity mapping (FCM) within the functional magnetic resonance imaging (fMRI) field, many studies have reported finding functionally connected networks, or temporally correlated brain regions. Many groups also report network changes in pathology, indicating potential diagnostic relevance for FCM. However, fMRI's blood oxygen level dependent (BOLD) signal, widely assumed to reflect underlying local neural activity, is in fact a measurement of local concentration changes in deoxy-hemoglobin, complicating interpretation of FCM results. Nevertheless, most human FCM studies (as well as animal studies) have found networks that are consistent across sample groups, bilaterally symmetric and often correspond to known anatomical regions.
In a recent study, we used wide-field optical mapping (WFOM) to capture both excitatory neural activity (in Thy1-GCaMP6f mice) and hemodynamics across the entire dorsal surface of the awake, behaving mouse brain [1]. WFOM revealed striking patterns of bilaterally symmetric resting state neural activity that we demonstrated to be correlated to spontaneous fluctuations in hemodynamics. We propose that these patterns of neural activity may represent the underlying neural basis of resting state fMRI. Our direct, high speed view of this spontaneous neural activity provides a far more detailed picture of its properties than the noisier and spatiotemporally filtered representation provided by fMRI. We can therefore apply a range of analysis methods to begin to

characterize this activity to gain a clearer picture of its drivers, dependencies and the governing properties of its spatiotemporal dynamics. Here we will present our progress towards developing mathematical models of this spontaneous activity, focusing demonstrating whether the activity better fits with a model of wave-like propagation across the cortex, or stationary spatial representations that fluctuate over time. Our results could provide new approaches to information extraction in resting state fMRI, as well as new understanding of the origins and role of brain-wide spontaneous activity in relation to ongoing brain function.

1. Ma Y., Shaik M.A., Kozberg M.G., Kim S.H., Portes J.P., Timerman D., and Hillman E.M.C., Resting-state hemodynamics are spatiotemporally coupled to synchronized and symmetric neural activity in excitatory neurons. Proceedings of the National Academy of Sciences, 2016.

Disclosures: S.H. Kim: None. **M.A. Shaik:** None. **Y. Ma:** None. **H.T. Zhao:** None. **D.N. Thibodeaux:** None. **M. Khabbazian:** None. **T. Zheng:** None. **E.M. Hillman:** None.

Poster

093. Functional Monitoring and Stimulation

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Topic: I.06. Computation, Modeling, and Simulation

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Title: Computing brain signals (CBra): Concurrent simulation of network activity, extracellular electric potentials and magnetic fields

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Abstract: Recordings of extracellular electrical, and later also magnetic, brain signals have been the dominant technique for measuring brain activity for decades. The interpretation of such signals is however nontrivial [1], as the measured signals result from both local and distant neuronal activity. In volume-conductor theory the recorded extracellular potentials stem from a complicated sum of contributions from transmembrane currents of neurons near the measurement site. Further, given the same transmembrane currents the contributions to the magnetic field recorded outside the brain can be computed [2]. This allows for the development of computational tools implementing forward models grounded in the biophysics underlying the different measurement modalities [1].

LFPy ([3], LFPy.github.io) incorporated a now well-established scheme for predicting extracellular potentials of individual neurons with arbitrary levels of biological detail. It relies on NEURON ([4], neuron.yale.edu) to compute transmembrane currents of multicompartment neurons which is then used in conjunction with an electrostatic forward model [5]. We have now extended its functionality to populations and networks of multicompartment neurons with concurrent calculations of extracellular potentials and current-dipole moments. The current-dipole moments are used to compute non-invasive measures of neuronal activity, like magnetoencephalographic (MEG) signals [2,6] and, when combined with an appropriate head-model, electroencephalogram (EEG) scalp potentials. One such built-in head-model is the 4-sphere model including the different electric conductivities of brain, cerebral spinal fluid, skull and scalp [6].
The version of LFPy presented here is thus a true multi-scale simulator, capable of simulating electric neuronal activity at the level of cell-membrane dynamics, individual synapses, neurons, networks, extracellular potentials within neuronal populations and macroscopic EEG and MEG signals. The present implementation is equally suitable for execution on laptops and in parallel on high-performance computing (HPC) facilities.
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2. Hämäläinen M et al. Rev Mod Phys 1993, 65:413-487
3. Lindén H et al. Front Neuroinf 2014, 7(41):1-15
4. Hines ML et al. Front Neuroinf 2009, 3(1):1-12
5. Holt G & Koch C. J Comp Neurosci 1999, 6:169-184
6. Nunez PL & Srinivasan R. Electric Fields of the Brain. Oxford University Press 2006

Disclosures: **E. Hagen:** None. **S. Næss:** None. **T.V. Ness:** None. **G.T. Einevoll:** None.

Poster

093. Functional Monitoring and Stimulation

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Title: Brain vessels segmentation for light-sheet microscopy image using convolutional neural networks

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Abstract: Brain vessel segmentation is an important step in image analysis for function and disease studies. To extract all the cerebrovascular patterns, including arteries and capillaries, some filter-based methods are used to segment vessels. However, the design of accurate and robust vessel segmentation algorithms is still challenging, due to the variety and complexity of images, especially in Brain blood vessel segmentation. In this work, we addressed a problem of automatic and robust segmentation of Brain micro-vessels structures in cerebrovascular images acquired by light-sheet microscope for mouse. To segment micro-vessels in large-scale image data, we proposed a convolutional neural networks (CNNs) architecture trained by 1.58 million pixels with manual label. Three convolutional layers and one fully connected layer were used in the CNNs model. We extracted a patch of size 32x32 pixels in each acquired vessel image as training data set to feed into CNNs for classification. This network was trained to output the probability that the center pixel of input patch belongs to vessel structures. To build the CNNs architecture, a series of mouse vascular images acquired from a commercial light sheet fluorescence microscopy (LSFM) system were used for training the model. The experimental results demonstrated that our approach is a promising method for effectively segmenting micro-vessels structures in cerebrovascular images with vessel-dense, nonuniform gray-level and long-scale contrast regions.

Disclosures: **H. Hui:** None. **X. Yang:** None. **C. Hu:** None. **S. Wang:** None. **J. Tian:** None.

Poster

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Title: A two-photon microscopy simulation framework for optimizing optics and benchmarking cell-finding algorithms

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Abstract: The widespread adoption of two-photon microscopy (TPM) for imaging of neural activity at cellular resolution has spurred the development both of novel optics configurations and automated cell-finding algorithms. These developments have increased the number of recorded neurons, which is important for population level analysis of neural circuit function. Despite these advances, optimization of the optics and validation of the algorithms remains difficult. Microscope parameters are typically laboriously hand-tuned and empirically tested for useful configurations, trading off point-spread function (PSF) geometry and signal/noise ratios (SNR). Currently, automated cell-finding algorithms are validated by comparing identified neural profiles ("cell shapes") to manually located profiles, and "ground-truth" calcium transients obtained via simultaneous electrophysiology recordings are unavailable outside of a few specific configurations. Here we describe a detailed TPM simulation framework for optimizing microscope parameters and validating automated algorithms *in silico*. First, we generate neural volumes including vasculature, neurons, and neurites, using parameters matched to biophysical measurements. Neural somas are modeled as isotropic Gaussian processes and stochastic path-planning algorithms are used to grow vasculature, dendrites, and other processes. Second, we simulate each neuron's (and each component of neuropil's) spiking activity either by simulating spontaneous activity or reproducing a predetermined user-defined activity. Calcium fluorescence is then simulated from spikes using a biophysical model for calcium and indicator dynamics for each of the neural somas and processes. Third, the PSF is generated and scattering/occlusion effects in tissue are computed. Fourth, the resulting volume is scanned with in a simulation that includes brain motion and a photon noise model including electronic and detector response contributions. We demonstrate our framework by simulating diffraction-limited TPM calcium fluorescence data from L2/3 of mouse visual cortex. We use this simulation to assess the performance of automated cell-finding algorithms in a suite of quality criteria including replication of calcium signals, elimination of crosstalk between cells, and robustness against motion artifacts. In addition, we estimate the relationship between optical parameters such as scan area and PSF size and signal fidelity. We anticipate that our simulation framework will streamline microscope and algorithm development, improving strategic co-development of optics and algorithms.

Disclosures: **A. Song:** None. **A.S. Charles:** None. **D.W. Tank:** None. **J.W. Pillow:** None.

Poster

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Title: Inference of *C. elegans* whole brain interaction with a minimal pairwise probability model

Authors: *X. CHEN[1], A. N. LINDER[2], J. P. NGUYEN[1], A. M. LEIFER[1,2], W. BIALEK[1,3]
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Abstract: Recent technological development has allowed simultaneous measurement of large population of neurons in freely-behaving animals. In order to understand the correlated spiking activities, pairwise probabilistic models constructed with methods of maximum entropy have been developed and have found much success in studying many neuronal systems including retina and hippocampus. Here, using Caenorhabditis elegans as our model system, we show that this formalism can be generalized by mapping the neuronal activities to q-state Potts model to describe 1) neural networks with graded potential and 2) systems of neurons with size close to that of the whole brain. We find that the pairwise interactions account for higher-order correlations, and that the network exhibits collective states similar to the ones of spin glasses.

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Poster

093. Functional Monitoring and Stimulation

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Support: NIH NIBIB R01EB018297

University of Michigan MICDE Grant

Title: Measuring learning-induced changes in neural networks using functional network stability under changing network topology and excitatory/inhibitory balance

Authors: *Q. SKILLING[1], D. MARUYAMA[2], N. OGNJANOVSKI[5], S. J. ATON[3], M. R. ZOCHOWSKI[4]
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Abstract: Contextual fear conditioning creates fear memories (CFMs), in mice, which are consolidated and can be reactivated after a single training session. In previous work, we showed both experimentally and computationally that CFMs can be reliably detected through high Functional Network Stability (FuNS), an algorithm developed to determine changes in functional connectivity. Here, we examine computationally how FuNS can be used to detect learning-induced dynamic changes in the context of different network topologies in systems with varying levels of excitation and inhibition. We model networks with changing connectivity degree, locality, and strength using the leaky integrate-and-fire (LIF) formalism. Hebbian learning in the form of spike-timing dependent plasticity is used in conjunction with acute network input to classify the robustness of network response to strong incoming information, e.g. due to contextual fear conditioning. Results show that FuNS (1) is robust to changes in network topology in excitatory only networks and (2) is greatest near a balance of excitatory and inhibitory inputs.

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Poster

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Title: Characterization of ‘Intensity of Detection’ isocontours in a single photon fiber photometry system

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Abstract: While two photon fluorescent imaging (TPI) of calcium (Ca2+) dynamics has witnessed vast advances over the past few years it is still constrained by the limited penetration depth of the optical excitation, impeding the ability to study large neuronal ensembles distributed across multiple, deep brain structures. In contrast, single photon, multimode fiber-based photometry allows monitoring the aggregate activity of a large population of cells from brain areas that are not readily accessible with TPI. Properties of light emanating from a fiber has been studied in brain slices along and across the direction of light propagation to quantify the volume of tissue activated by the excitation light within hypothetical contours of influence. Neurons within this volume may emit fluorescent signals that will propagate to the tip of the fiber. Transmission properties of the emitted fluorescence-which define the strength by which each neuron's activity is detected at the fiber tip-remain to be quantified.
Here, we define the 'intensity of detection' (IoD) isocontours of a multimode fiber using the basic formulation of the cone of acceptance and the actual optical properties of a tissue volume of the adult rat brain. We built a brain phantom that closely mimic the optical transmittance characteristics of the brain in the visible (350-700 nm) range, and that contains fluorescent beads (dia=15um, 505/515nm) that would allow discerning a single bead. A multimode fiber (r=200um, NA=0.48), connected to a 473nm LED, was then lowered into the brain phantom and moved with respect to a single bead to scan the entire volume above an arbitrarily selected bead. The intensity of the fluorescence detected by the fiber was recorded and the IoD contours were calculated. These were are subsequently validated in a culture of GCamP6f expressing pyramidal neurons.
We found that the detected fluorescence intensity largely decreased beyond 100um in the transverse direction (half the radius) from the center of the fiber. This suggests that the detection contours might differ from the cone of influence contours suggested by other groups. Defining IoD contours based on realistic optical properties may improve the ability to estimate of the number of sources contributing to a fiber photometry signal and help develop a model that relates the strength of each contributing signal source to its spatial location in the cone of acceptance.

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Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: ERC Consolidator BrainMicroFlow 615102

Calmip Projet P1541

Title: Towards a large-scale simulation of blood flow in brain microcirculation

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Abstract: The human brain microcirculation has a multiscale architecture. At large scale, arteriolar and venular trees supply the cerebral cortex with blood carrying oxygen and nutrients, and drain the metabolic waste. At small scale, the capillary vessels constitute a mesh-like network that connects the larger trees. They are embedded in the cerebral tissue and control most of the mass transfer toward the neurons.
For the last decades, network approaches have significantly advanced our understanding of blood flow, mass transport and regulation mechanisms. However, because of the huge number of capillaries, these approaches cannot be used in large cortical volumes, which are clinically relevant.
Here, we develop a hybrid approach for modeling blood flow by replacing the dense and space-filling capillary bed by a porous medium, defined by effective properties (e.g. permeability) at coarser scale. The arteriolar and venular networks are still represented by a network approach because of their quasi-fractal structure. To couple both frameworks, we use an approach similar to Peaceman, SPE/AIME, 1978. This model is based on an analytical approximation describing the strong pressure gradients building up in the vicinity of the arterio- and venulo-capillary coupling points.
Fig. 1 compares the results obtained from the present approach (black) with those from a standard network approach (orange), showing a very good agreement. In contrast, not taking into account the local pressure gradients, i.e. using a simple condition of pressure continuity at coupling points (gray) results in large errors.

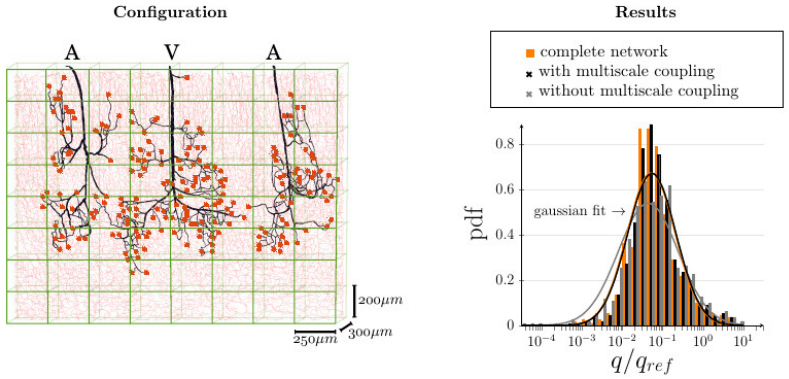

Figure 1: **Left:** the capillary bed (light red) is replaced by a porous medium discretized on a coarse grid (green). This continuum is characterized at larger scale by effective properties obtained from known or statistical data, using volume averaging (Davit et al, Adv Water Resour, 2013). Coupling points are highlighted by red dots. **Right:** distribution of flow rates in the arteriolar and venular vessels displayed on the left-hand side: comparison between a standard network approach (Lorthois et al, NeuroImage, 2011) and the present hybrid approach.

The hybrid approach also yields a huge gain in computation time (several orders of magnitude for the network in Fig. 1). It has further been implemented in a code designed for high performance computing. Assuming that sufficient skeletonized anatomical data (arterioles and venules) will be available in the future (Errico, Nature, 2015), this approach paves the way for simulating blood flow and mass transfers in the whole brain, with perspectives for absolute blood flow quantification in perfusion imaging.

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Poster

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Austrian Research Promotion Agency (FFG)

Title: Predicting brain functional maps from genetic information

Authors: *W. E. HAUBENSAK[1], F. GANGLBERGER[2], J. KACZANOWSKA[1], J. M. PENNINGER[3], A. HESS[4], K. BÜHLER[2]
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Abstract: Linking genetic information to brain anatomy allows for the computational exploration of molecular-to-systems level organization of brain function. Here, we fused publicly available brain gene expression maps and connectivity data with functionally related gene sets. We find that the functional genetic load accumulates in specific nodes in the brain and associates neuronal networks with specific multigenic functions. These maps recapture known functional anatomical annotations from literature and functional MRI data. When applied to meta data from mouse QTLs and human neuropsychiatric databases, our method predicts functional maps underlying behavioral or psychiatric traits. We show that it is possible to predict functional neuroanatomy from mouse and human genetic meta data and provide a discovery tool for high throughput functional exploration of brain anatomy in silico.

Disclosures: W.E. Haubensak: None. **F. Ganglberger:** None. **J. Kaczanowska:** None. **J.M. Penninger:** None. **A. Hess:** None. **K. Bühler:** None.

Poster

093. Functional Monitoring and Stimulation

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Title: Improving the accuracy of neural decoding of choice behavior with response time data and cognitive modeling

Authors: *B. BARIBAULT, J. VANDEKERCKHOVE
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Abstract: If neural data come from a motor planning or decision accumulator area, neural decoding techniques may be used to predict a behavioral response from the neural data alone. We have developed a new approach to neural decoding of behavior called neurocognitive process models (NPMs). This novel approach is defined by the simultaneous implementation of a behavioral model and a neural model as a single hierarchical Bayesian graphical model. NPMs not only allow for accurate behavioral predictions, but also allow for many parameters with meaningful semantic interpretations, such as response bias, to be estimated at the same time. These parameters may subsequently be used as the basis for further inference.
For this project, we developed two versions of a NPM: one which only models the decision choice, and another which models both the choice and the response time. The latter version incorporated the drift diffusion model, a well-established cognitive model of reaction time, as the behavioral component. We compared the performance of these NPMs to logistic regression by observing differences in accuracy in predictions of the decision, accuracy in predictions of response time, fit to data, and ability to explain the underlying neurocognitive process.
All approaches were applied to an open dataset collected by Feierstein, Quirk, Uchida, Sosulski, and Mainen (2016). In their behavioral task, rats performed a 2AFC odor discrimination task in which they reported which of two scents was presented by licking a port to the left or the right of the scent port. During the task, extracellular recordings were taken from orbitofrontal cortex, which the original findings suggest encodes the upcoming decision (i.e., the direction of the licking movement).
The NPMs and logistic regression were all able to successfully make out-of-sample predictions of rats' choice behavior from preparatory neural data (50/50 split of trials across train and test). Critically, we observed that including response time in the prediction process provided a significant bump in decoding ability, as measured by the increase in choice prediction accuracy. While the rate of prediction of the NPMs did not surpass logistic regression, the NPM did offer

unique insight into the underlying neurocognitive process, allowing us to quantify cognitive factors, such as the response bias of individual rats, separately from neural factors.
We discuss how this novel decoder may be easily altered to accommodate different experimental contexts, and thus may be viewed as a generalizable approach to neural decoding of behavior in a Bayesian framework.

Disclosures: **B. Baribault:** None. **J. Vandekerckhove:** None.

Poster

093. Functional Monitoring and Stimulation

Location: Halls A-C

Time: Saturday, November 11, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 093.21/VV12

Topic: I.06. Computation, Modeling, and Simulation

Support: U.S. Army Research Office W911NF1410141

Title: Superpixels based landmarks tracking for biomechanics applications

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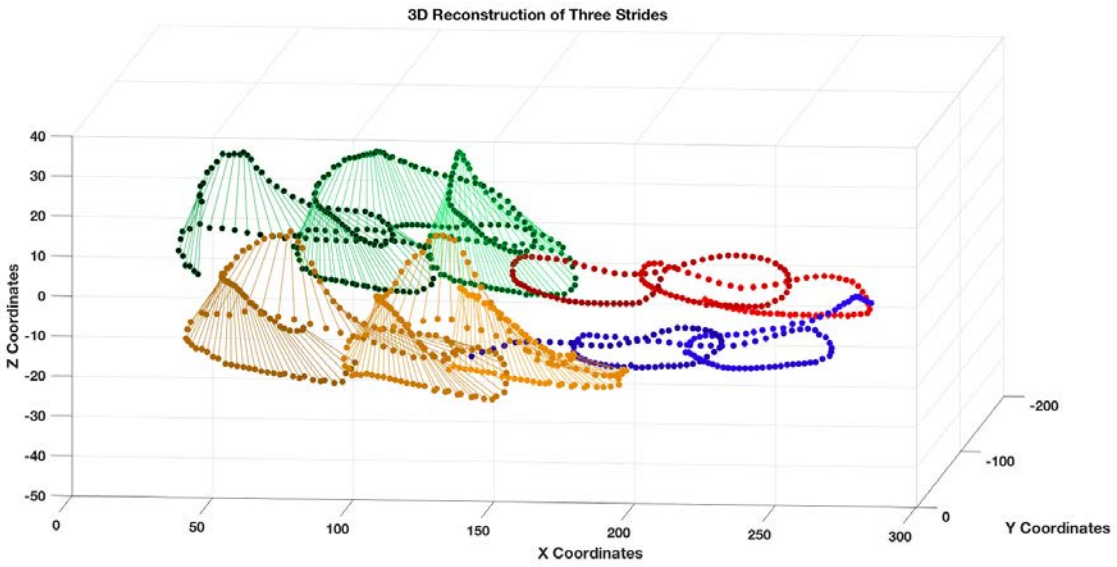
Abstract: Locomotion is crucial to survival and reproduction in most animals. In addition, examining locomotion has improved our basic understanding of motor control and aided in treating motor impairment. Mice are a premier model of human disease and increasingly the model system of choice for basic neuroscience. High frame rates (250 Hz) are needed to quantify the kinematics of running mice, due to their high stride frequency (up to 10 Hz). Thus, manual tracking, especially for multiple landmarks, becomes time-consuming and impossible for large sample sizes; therefore, an automated method is necessary.
One approach to this problem has been to attach retroreflective markers to the body of the animal, and use standard optical motion capture systems. While commercial systems exist (e.g. Digigait, Motorater, and Noldus Catwalk) that are able to perform markerless tracking of specific landmarks on the body, they are expensive and typically designed for specific applications.
Here we present a method for automatic tracking of landmarks on the body of moving rodents, including the paws. We validated the algorithm with video from four cameras surrounding a custom-made treadmill system. A primary difficulty of automatic tracking from video is handling of occlusions; here we find that super-pixel based segmentation in conjunction with classification via a probabilistic function can greatly mitigate this problem. The probabilistic function used kinematic and color features (e.g. speed, direction of movement, size, shape, color information) to classify the segmented regions. Finally, 3D reconstruction of the tracked landmarks was generated using a direct linear transform. This tool can be used in different settings, including treadmills, arenas, or over ground track-way studies. Figure

illustrates the 3D reconstruction of paw movement for these data.
Figure 1 shows 3D reconstruction of the tracked paw for three strides of rat treadmill locomotion. The direct linear transform (DLT) method was used to reconstruct the 3D coordinates.



Disclosures: **O. Haji Maghsoudi:** None. **A. Vahedipour:** None. **B.D. Robertson:** None. **A. Spence:** None.

Poster

093. Functional Monitoring and Stimulation

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Title: A 3D visualization tool for invasive electrodes spatial-temporal localization using fMRI, EEG and MEG

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Abstract: In recent years, there have been significant advancements in real-time closed-loop electrophysiology. The implantation of invasive electrodes, which was usually done for locating the epileptic source, can be utilized nowadays also for implementation of dual-purpose electrodes for recording and stimulating. This kind of technology brought into play a better brain-machine interface allowing the clinician to apply precise stimulation based on neuronal recorded activity. Furthermore, this manipulation will utilize new forms of treatment for psychiatric diseases, like PTSD. Surgeries which use these dual-purpose electrodes are extremely challenging because they require multiple components to work in sync. First, finding precise spatial-localization of the desired source is required. For example, in the context of psychiatric diseases, the source is the location of an abnormal activity, compared to the healthy population. Second, for a stimulation to become effective, not only the location is needed, but also the exact timing - the epileptic seizure onset in the epileptic case, The sensory and motor activation for brain-machine interface, and the neuronal activity deviants from a healthy population pattern in the case for psychiatric diseases. To pinpoint this location precisely, both in the spatial and temporal domains, a multi-modality neuroimaging approach is needed - an approach which integrated data from multiple modalities, such as EEG, MEG, and fMRI. In this work, we present a 3D visualization tool, which presents and analyze results from all of these modalities. Results are integrated and shown into the subject's native MRI space. Furthermore, the use of invasive electrodes is integrated directly into the tool, so the recorded intracranial activity can be viewed and analyzed alongside with the neuroimaging data.

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